Gastroenteritis in children

Search date March 2010

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ABSTRACT

INTRODUCTION: Acute gastroenteritis results from infection of the gastrointestinal tract, most commonly with a virus. It is characterised by rapid onset of diarrhoea with or without vomiting, nausea, fever, and abdominal pain. Diarrhoea is defined as the frequent passage of unformed, liquid stools. Regardless of the cause, the mainstay of management of acute gastroenteritis is provision of adequate fluids to prevent and treat dehydration. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent acute gastroenteritis in children? What are the effects of treatments for acute gastroenteritis in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 42 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of: rotavirus vaccines for the prevention of gastroenteritis; enteral rehydration solutions (oral or gastric), lactose-free feeds, loperamide, probiotics, and zinc for the treatment of gastroenteritis; and ondansetron for the treatment of vomiting.

QUESTIONS

INTERVENTIONS

Key points

- Gastroenteritis in children worldwide is usually caused by rotavirus, which leads to considerable morbidity and mortality.

  Bacterial causes of gastroenteritis are more common in developing countries.
- Rotavirus vaccines are both safe and effective in preventing and minimising harm from gastroenteritis caused by rotavirus, particularly in preventing severe disease.
- Enteral rehydration solutions containing sugar or food plus electrolytes are as effective as intravenous fluids at correcting dehydration and reducing the duration of hospital stay, and may have fewer major adverse effects.
- Lactose-free feeds may reduce the duration of diarrhoea in children with mild to severe dehydration compared with feeds containing lactose, but studies have shown conflicting results.
- Loperamide can reduce the prevalence of acute diarrhoea in children in the first 48 hours after initiation of treatment, but there is an increased risk of adverse effects compared with placebo.
- Ondansetron reduces vomiting but increases diarrhoea in children with gastroenteritis compared with placebo.
- Zinc may reduce the duration of diarrhoea compared with placebo but may also increase the risk of vomiting; most studies were conducted in developing countries, with little evidence from developed countries.
- Probiotics may reduce the duration of diarrhoea and may reduce hospital stay, with most evidence for *Lactobacillus* species.

DEFINITION Acute gastroenteritis results from infection of the gastrointestinal tract, most commonly with a virus. It is characterised by rapid onset of diarrhoea with or without vomiting, nausea, fever, and abdominal pain. [1] In children, the symptoms and signs can be non-specific. [2] Diarrhoea is defined as

the frequent passage of unformed, liquid stools. [3] Regardless of the cause, the mainstay of management of acute gastroenteritis is provision of adequate fluids to prevent and treat dehydration. The WHO also recommends administration of oral zinc. [4] In this review, we examine the benefits and harms of interventions to prevent and treat gastroenteritis, irrespective of its cause.

INCIDENCE/ PREVALENCE

Worldwide, diarrhoea causes the death of about 2 million children under 5 years of age each year; [5] of these deaths, up to 600,000 are caused by rotavirus. [6] Gastroenteritis leads to hospital admission in 7/1000 children under 5 years of age each year in the UK, [7] and diarrhoea results in hospital admission in 1/23 to 1/27 children in the US by the age of 5 years. [8] In Australia, gastroenteritis accounts for 6% of all hospital admissions in children under 15 years. [9] Acute gastroenteritis accounts for 204/1000 general practitioner consultations in children under 5 years in the UK. [7] In the US, rotavirus results in hospital admission in 1/67 to 1/85 children by the age of 5 years. [8]

AETIOLOGY/ RISK FACTORS

In developed countries, acute gastroenteritis is predominantly caused by viruses (87%), of which rotavirus is the most common. [9] [10] [11] [12] [13] Worldwide, rotavirus causes almost 40% of cases of severe diarrhoea in infants. [14] Rotavirus outbreaks show a seasonal pattern in temperate climates, and infections peak during winter months. In countries closer to the equator, seasonality is less noticeable, but the disease is more pronounced in the drier and cooler months. The reason for rotavirus seasonality is not known. Bacteria, predominantly *Campylobacter*, *Salmonella*, *Shigella,* and *Escherichia coli*, cause most of the remaining cases of acute gastroenteritis. In developing countries, where bacterial pathogens are more prevalent, rotavirus is still a major cause of gastroenteritis; 82% of worldwide deaths caused by rotavirus occur in these countries. [6]

PROGNOSIS

Acute gastroenteritis is usually self-limiting, but if untreated it can result in morbidity and mortality secondary to water loss, and electrolyte and acid–base disturbance. Acute diarrhoea causes 4 million deaths each year in children aged under 5 years in Asia (excluding China), Africa, and Latin America, and more than 80% of deaths occur in children under 2 years of age. [15] Although death is uncommon in developed countries, dehydration secondary to gastroenteritis is a significant cause of morbidity and hospital admission. [9] [10] [16]

AIMS OF INTERVENTION

To prevent gastroenteritis; to prevent diarrhoea in children with gastroenteritis; to reduce the duration of diarrhoea, quantity of stool output, and duration of hospital stay; to prevent and treat dehydration; to promote weight gain after rehydration; to prevent persistent diarrhoea associated with lactose intolerance in children with gastroenteritis of any cause; and to prevent vomiting.

OUTCOMES

***Prevention:* episodes of diarrhoea; admissions to hospital; mortality; adverse effects (including adverse effects requiring admission to hospital, life-threatening adverse effects, intussusception, gastrointestinal adverse effects, fever, irritability, and general adverse effects). *Treatment:* duration of diarrhoea** (time until permanent cessation); **admissions to hospital; duration of hospital stay; mortality; total stool volume; weight gain** after rehydration; **adverse effects**. For the antiemetic ondansetron, we additionally report episodes of vomiting with minimal adverse effects of treatment.

METHODS

Clinical Evidence search and appraisal March 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2010, Embase 1980 to March 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 1 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 62). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any

individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to prevent acute gastroenteritis in children?**

OPTION **ROTAVIRUS VACCINES**

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Rotavirus vaccines are both safe and effective in preventing and minimising harm from gastroenteritis caused by rotavirus, particularly in preventing severe disease.

Benefits and harms

Rotavirus vaccines versus placebo:

We found two systematic reviews (search date 2003, 64 RCTs; [17] and search date 2007, 10 RCTs [18]) and two additional [19] [20] and 8 subsequent RCTs [21] [22] [23] [24] [25] [26] [27] [28] comparing rotavirus vaccines versus placebo; one RCT in the second review was reported in two papers. [19] [29] The first systematic review examined rhesus rotavirus vaccines, live-attenuated bovine rotavirus vaccines, and human attenuated rotavirus vaccines. [17] However, the tetravalent rhesus rotavirus vaccine was voluntarily withdrawn from the market in October 1999 because of an association with intussusception, [30] and the monovalent rhesus rotavirus vaccine is not licensed, so only data for live-attenuated bovine rotavirus vaccines and human attenuated rotavirus vaccines are reported here. Owing to significant heterogeneity, the second review [18] did not perform a meta-analysis, so we report results from individual RCTs here. Of the included RCTs, two large RCTs assessed the safety and efficacy of human–bovine and human rotavirus vaccines in >60,000 children each. [31] [32] One included RCT assessed the rhesus rotavirus tetravalent vaccine that has subsequently been withdrawn and therefore the details of this study are not included here. [33] The other RCTs included in the reviews [29] [34] [35] [36] [37] and the two additional [19] [20] and 8 subsequent RCTs [21] [22] [23] [24] [25] [26] [27] [28] we identified assessed different combinations and dosages of the vaccines using a variety of outcomes. One RCT identified by the second review [18] compared both bovine–human rotavirus reassortant tetravalent vaccine (2 doses) and rhesus–human rotavirus reassortant tetravalent vaccine versus placebo; we report only data for the bovine–human rotavirus reassortant tetravalent vaccine versus placebo. [38]

Episodes of diarrhoea

Compared with placebo Rotavirus vaccines seem more effective at decreasing episodes of diarrhoea caused by rotavirus. Results varied with the specific vaccine used (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of children with episodes of diarrhoea from any cause					
[17] Systematic review	2703 healthy children aged 1.5 to 60 months 6 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Proportion of children with episodes of diarrhoea from any cause , 6 to 15 months** 27/140 (19%) with human attenuated rotavirus vaccine 30/141 (21%) with placebo 281 children in this analysis	RR 0.91 95% CI 0.57 to 1.44	⟷	Not significant
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela The 4 arms of the RCT compared human strain	**Episodes of diarrhoea from any cause , until 1 year of age** 1216 episodes in 1392 children with pooled vaccine group (human strain RIX4414 $10^{4.7}$ffu, $10^{5.2}$ffu, and $10^{5.8}$ffu vaccines; all 2 doses) 419 episodes in 454 children with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	RIX4414 10 $^{4.7}$ focus-forming units (ffu), 10 $^{5.2}$ ffu, and 10 $^{5.8}$ ffu vaccines versus placebo	Data for individual vaccine doses not reported			
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Proportion of children with episodes of diarrhoea from any cause , until 18 months of age** 98/501 (20%) with human strain RIX4414 10 $^{4.7}$ ffu vaccine (2 doses) 85/639 (13%) with human strain RIX4414 10 $^{5.2}$ ffu vaccine (2 doses) 93/639 (15%) with human strain RIX4414 10 $^{6.1}$ ffu vaccine (2 doses) 111/642 (17%) with placebo	Significance not assessed		
[17] Systematic review	3309 healthy children aged from newborn to 60 months 11 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Proportion of children with episodes of diarrhoea from any cause , 1 week to 32 months** 523/1797 (29%) with live-attenuated bovine rotavirus vaccine 572/1512 (38%) with placebo	RR 0.73 95% CI 0.60 to 0.89	●○○	live-attenuated bovine rotavirus vaccine
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland Intention-to-treat (ITT) analysis of entire population	**Proportion of children with episodes of diarrhoea from any cause , 7 to 21 months** 84/172 (49%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 68/86 (80%) with placebo	Vaccine efficacy 38% 95% CI 25% to 49% P <0.001	○○○	bovine–human rotavirus reassortant tetravalent vaccine
[19] [29] RCT **4-armed trial**	1846 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela The 4 arms of the RCT compared human strain RIX4414 10 $^{4.7}$ ffu, 10 $^{5.2}$ ffu, and 10 $^{5.8}$ ffu vaccines versus placebo	**Proportion of children with episodes of diarrhoea from any cause , until 1 year of age** 573/1392 (41%) with pooled vaccine group (human strain RIX4414 10 $^{4.7}$ ffu, 10 $^{5.2}$ ffu and 10 $^{6.1}$ ffu vaccines; all 2 doses) 214/454 (47%) with placebo Data for individual vaccine doses not reported	Significance not assessed		
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Proportion of children with episodes of diarrhoea from any cause , 18 to 22 months** 66% with human strain RIX4414 (2 doses)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		65% with placebo Absolute numbers not reported			
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea from any cause , 1 year** with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) with placebo Absolute results not reported Results from the first rotavirus season	Vaccine efficacy 98% 95% CI 88.3% to 100%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
Proportion of children with severe episodes of diarrhoea from any cause					
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Proportion of children with severe episodes of diarrhoea from any cause , until 18 months of age** 2/501 (0.4%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 4/639 (0.6%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 5/639 (0.8%) with human strain RIX4414 $10^{6.1}$ffu vaccine (2 doses) 10/642 (2%) with placebo	Significance not assessed		
[17] Systematic review	714 healthy children aged from newborn to 60 months 3 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Proportion of children with severe episodes of diarrhoea from any cause , 1 week to 32 months** 39/398 (10%) with live-attenuated bovine rotavirus vaccine 69/316 (22%) with placebo	RR 0.51 95% CI 0.21 to 1.26	⟷	Not significant
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Proportion of children with severe episodes of diarrhoea from any cause , 7 to 21 months** 1/172 (0.6%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 5/86 (6%) with placebo	Vaccine efficacy 90% 95% CI 35% to 99% P = 0.012	○○○	bovine–human rotavirus reassortant tetravalent vaccine
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic,	**Proportion of children with severe episodes of diarrhoea from any cause , until 1 year of age** 183/9009 (2%) with human strain RIX4414 (2 doses) 300/8858 (3%) with placebo	Vaccine efficacy 40% 95% CI 27.7% to 50.4% RR 0.60 CI not reported	○○○	human strain RIX4414

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela				
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Proportion of children with severe episodes of diarrhoea from any cause , 18 to 22 months** 5% with human strain RIX4414 (2 doses) 9% with placebo Absolute numbers not reported	Significance not assessed		
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Proportion of children with severe episodes of diarrhoea from any cause , until 18 months of age** 74/501 (15%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 73/639 (11%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 84/639 (13%) with human strain RIX4414 $10^{6.1}$ffu vaccine (2 doses) 100/642 (16%) with placebo	Significance not assessed		
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, but principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea from any cause , 5.7 to 12 months** 256/2572 (10%) with $10^{6.5}$ffu vaccine 257/1302 (20%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 49.6% 95% CI 39.8% to 57.8%	○○○	$10^{6.5}$ffu vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Proportion of children with episodes of severe gastroenteritis from any cause , 2 weeks after vaccination until aged 1 year** 256/2974 (9%) with human rotavirus vaccine 178/1443 (12%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Vaccine efficacy 30.2% 95% CI 15.0% to 42.6% P <0.001	○○○	human rotavirus vaccine
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea from any cause , up to age 2 years** 141/5263 (3%) with human attenuated rotavirus vaccine $10^{6.5}$ffu 202/5256 (4%) with placebo	Vaccine efficacy 30.3% 95% CI 13.1% to 44.2% P <0.001	○○○	human attenuated rotavirus vaccine $10^{6.5}$ffu

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of children with episodes of diarrhoea caused by rotavirus					
[17] Systematic review	2482 healthy children aged 1.5 to 60 months 3 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus , 6 to 15 months** 67/1730 (4%) with human attenuated rotavirus vaccine 91/752 (12%) with placebo	RR 0.42 95% CI 0.21 to 0.85	●●○	human attenuated rotavirus vaccine
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Proportion of children with episodes of diarrhoea caused by rotavirus , until 18 months of age** 2/501 (0.4%) with human strain RIX4414 $10^{4.7}$ ffu vaccine (2 doses) 0/639 (0%) with human strain RIX4414 $10^{5.2}$ ffu vaccine (2 doses) 0/639 (0%) with human strain RIX4414 $10^{6.1}$ ffu vaccine (2 doses) 4/642 (0.6%) with placebo	Pooled vaccine efficacy 82% CI not reported P = 0.046 for among-group comparison	○○○	pooled vaccine
[17] Systematic review	5283 healthy children aged from newborn to 60 months 17 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Proportion of children with episodes of diarrhoea caused by rotavirus , 1 week to 32 months** 393/2967 (13%) with human attenuated rotavirus vaccine 413/2316 (18%) with placebo	RR 0.59 95% CI 0.45 to 0.76	●○○	human attenuated rotavirus vaccine
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Proportion of children with episodes of diarrhoea caused by rotavirus , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 11/187 (6%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 39/183 (21%) with placebo	Vaccine efficacy 74.6% 95% CI 49.5% to 88.3% P <0.001	○○○	quadrivalent human–bovine (WC3) reassortant rotavirus vaccine
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 to 9 months** 8/161 (5%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 13/80 (16%) with placebo Results from first rotavirus season	Vaccine efficacy 69% 95% CI 29% to 86% P = 0.006	○○○	bovine–human rotavirus reassortant tetravalent vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 to 21 months** 12/161 (7%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 15/80 (19%) with placebo Results from first and second rotavirus seasons	Vaccine efficacy 60% 95% CI 20% to 80% P = 0.015	○○○	bovine–human rotavirus reassortant tetravalent vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 months** 19/276 (7%) with high-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 43/264 (16%) with placebo Results from first rotavirus season Per-protocol analysis excluding participants without a case definition of rotavirus gastroenteritis	Vaccine efficacy 61.2% 95% CI 31.9% to 78.6% Vaccine efficacy for high-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	high-potency pentavalent human–bovine reassortant rotavirus vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 months** 12/237 (5%) with middle-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 43/264 (16%) with placebo Results from first rotavirus season Per-protocol analysis excluding participants without a case definition of rotavirus gastroenteritis	Vaccine efficacy 70.5% 95% CI 43.1% to 85.8% Vaccine efficacy for middle-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	middle-potency pentavalent human–bovine reassortant rotavirus vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 months** 20/253 (8%) with low-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 43/264 (16%) with placebo Results from first rotavirus season	Vaccine efficacy 53.8% 95% CI 19.7% to 74.2% Vaccine efficacy for low-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	low-potency pentavalent human–bovine reassortant rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	Per-protocol analysis excluding participants without a case definition of rotavirus gastroenteritis			
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 months** 14/198 (7%) with high-potency G1–G4 human–bovine reassortant rotavirus vaccine (3 doses) 43/264 (16%) with placebo Results from first rotavirus season Per-protocol analysis excluding participants without a case definition of rotavirus gastroenteritis	Vaccine efficacy 59.2% 95% CI 24.0% to 79.4% Vaccine efficacy for high-potency G1–G4 human–bovine reassortant rotavirus vaccine *v* placebo	○○○	high-potency G1–G4 human–bovine reassortant rotavirus vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus , 7 months** 27/270 (10%) with high-potency P1A monovalent human–bovine reassortant rotavirus vaccine (3 doses) 43/264 (16%) with placebo Results from first rotavirus season Per-protocol analysis excluding participants without a case definition of rotavirus gastroenteritis	Vaccine efficacy 41.6% 95% CI 3.4% to 65.3% Vaccine efficacy for high-potency P1A monovalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	high-potency P1A monovalent human–bovine reassortant rotavirus vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18]	**Proportion of children with episodes of diarrhoea caused by rotavirus , until 1 year of age**	P <0.001 for human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 58% 95% CI 29% to 76%	○○○	human strain RIX4414 $10^{4.7}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 10 $^{5.2}$ffu vaccine 2 doses and 10 $^{5.8}$ffu vaccine 2 doses	21/468 (4%) with human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses) 49/454 (11%) with placebo			
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 10 $^{4.7}$ffu vaccine 2 doses and 10 $^{5.8}$ffu vaccine 2 doses	**Proportion of children with episodes of diarrhoea caused by rotavirus , until 1 year of age** 22/460 (5%) with human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) 49/454 (11%) with placebo	P <0.001 for human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 56% 95% CI 25% to 75%	○○○	human strain RIX4414 10 $^{5.2}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 10 $^{4.7}$ffu vaccine 2 doses and 10 $^{5.2}$ffu vaccine 2 doses	**Proportion of children with episodes of diarrhoea caused by rotavirus , until 1 year of age** 15/464 (3%) with human strain RIX4414 10 $^{5.8}$ffu vaccine (2 doses) 49/454 (11%) with placebo	P <0.001 for human strain RIX4414 10 $^{5.8}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 70% 95% CI 46% to 84%	○○○	human strain RIX4414 10 $^{5.8}$ffu vaccine
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Proportion of children with episodes of diarrhoea caused by rotavirus , 18 to 22 months** 13/245 (5%) with human strain RIX4414 (2 doses) 23/123 (19%) with placebo	Vaccine efficacy 72% 95% CI 42% to 87% P <0.001	○○○	human strain RIX4414
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus , 1 year** 82/2207 (4%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 315/2305 (14%) with placebo Results from the first rotavirus season Per-protocol analysis	Vaccine efficacy 74% 95% CI 66.8% to 79.9%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , 5.7 to 12 months** 85/2572 (3%) with 10 $^{6.5}$ffu vaccine 204/1302 (16%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 78.9% 95% CI 72.7% to 83.8%	○○○	10 $^{6.5}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT	336 healthy infants aged 2 months Location: Colombia	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , 2 weeks after vaccination until age 13 months** 5/159 (3%) with 10 $^{6.7}$ffu vaccine 20/160 (13%) with placebo	Vaccine efficacy 74.84% 95% CI 30.93% to 92.62% P value not reported	○○○	10 $^{6.7}$ffu vaccine
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed 3 different concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 44/486 (9%) with pooled vaccine group (3 concentrations of human rotavirus vaccine) 24/149 (16%) with placebo 745/778 (96%) children included in per-protocol analysis 635 children in this analysis	Vaccine efficacy 43.8% 95% CI 3.4% to 66.6% P value not reported	○○○	pooled vaccine group
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 16/163 (10%) with 10 $^{4.7}$ffu vaccine 24/149 (16%) with placebo 745/778 (96%) children included in per-protocol analysis 312 children in this analysis NOTE: 95% CI reported as –19.6% to +9.7%, an interval that does not include the stated efficacy; the negative lower limit suggests a non-significant result	Vaccine efficacy 39.1% CI not clear P value not reported	⟷	Not significant
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 18/153 (12%) with 10 $^{5.2}$ffu vaccine 24/149 (16%) with placebo 745/778 (96%) children included in per-protocol analysis 302 children in this analysis	Vaccine efficacy +27.0% 95% CI –40.4% to +62.7%	⟷	Not significant
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 10/170 (6%) with 10 $^{5.8}$ffu vaccine 24/149 (16%) with placebo 745/778 (96%) children included in per-protocol analysis 319 children in this analysis	Vaccine efficacy 63.5% 95% CI 20.8% to 84.4%	○○○	10 $^{5.8}$ffu vaccine
[26] RCT	2686 infants aged 6 to 12 weeks Location: Europe	**Proportion of children with episodes of diarrhoea caused by rotavirus , up to age 2 years**	Vaccine efficacy 68.0% 95% CI 60.3% to 74.4%	○○○	pentavalent human–bovine reas-

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		112/1100 (10%) with pentavalent human–bovine reassortant rotavirus vaccine (2 doses) 338/1173 (29%) with placebo 2273/2686 (85%) infants included in per-protocol analysis	P value not reported		sortant rotavirus vaccine
[37] RCT	1312 healthy infants aged 6 to 12 weeks Location: US and Finland	**Number of infants with rotavirus gastroenteritis/days of follow-up , 1 rotavirus season** 15/77,929 with pentavalent human–bovine (WC3) vaccine (3 doses) 54/77,037 with placebo 1115/1312 (85%) children included in per-protocol analysis The RCT assessed pentavalent rotavirus vaccine "at the end of shelf life"	Vaccine efficacy 72.5% 95% CI 50.6% to 85.6% P value not reported	○○○	pentavalent human–bovine (WC3) vaccine
Proportion of children with episodes of diarrhoea caused by rotavirus of a specific G serotype					
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 wild-type serotype , until 1 year of age** 12/468 (3%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 6/460 (1%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 7/464 (2%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 30/454 (7%) with placebo	Significance not assessed		
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G2 serotype , until 1 year of age** 0/468 (0%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 0/460 (0%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 1/464 (0.2%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 3/454 (0.7%) with placebo	Significance not assessed		
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G3 serotype , until 1 year of age** 1/468 (0.2%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 0/460 (0%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 0/464 (0%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2/454 (0.4%) with placebo			
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G4 serotype , until 1 year of age** 0/468 (0%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 0/460 (0%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 1/464 (0.2%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 0/454 (0%) with placebo	Significance not assessed		
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G9 serotype , until 1 year of age** 8/468 (2%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 14/460 (3%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 7/464 (2%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 15/454 (3%) with placebo	Significance not assessed		
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus canine serotype , until 1 year of age** 0/468 (0%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 0/460 (0%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 0/464 (0%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 1/454 (0.2%) with placebo	Significance not assessed		
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus of an unknown serotype , until 1 year of age** 0/468 (0%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 2/460 (0.4%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 0/464 (0%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 0/454 (0%) with placebo	Significance not assessed		
[20] RCT	439 healthy infants aged 2 to 6 months	**Proportion of children with episodes of diarrhoea caused by rotavirus of a specific G**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Location: US	**serotype , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 10/187 (5%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 26/183 (14%) with placebo			
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Proportion of children with episodes of diarrhoea caused by rotavirus G2 serotype , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 1/187 (0.5%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 2/183 (1.1%) with placebo	Significance not assessed		
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Proportion of children with episodes of diarrhoea caused by rotavirus G3 serotype , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 0/187 (0%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 10/183 (5%) with placebo	Significance not assessed		
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Proportion of children with episodes of diarrhoea caused by rotavirus G4 serotype , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 0/187 (0%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 1/183 (0.5%) with placebo	Significance not assessed		
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus G1, G2, G3, or G4 serotype , 7 months** 13/303 (4%) with high-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 33/281 (12%) with placebo ITT analysis of participants who received 3 doses of vaccine	Vaccine efficacy 65.8% 95% CI 27.7% to 85.0% Vaccine efficacy for high-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	high-potency pentavalent human–bovine reassortant rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus G1, G2, G3, or G4 serotype , 7 months** 8/264 (3%) with middle-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 33/281 (12%) with placebo ITT analysis of participants who received 3 doses of vaccine	Vaccine efficacy 75.1% 95% CI 39.9% to 91.3% Vaccine efficacy for middle-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	middle-potency pentavalent human–bovine reassortant rotavirus vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine; high-potency P1A monovalent human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus G1, G2, G3, or G4 serotype , 7 months** 16/280 (6%) with low-potency pentavalent human–bovine reassortant rotavirus vaccine (3 doses) 33/281 (12%) with placebo ITT analysis of participants who received 3 doses of vaccine	Vaccine efficacy 53.1% 95% CI 5.3% to 77.9% Vaccine efficacy for low-potency pentavalent human–bovine reassortant rotavirus vaccine *v* placebo	○○○	low-potency pentavalent human–bovine reassortant rotavirus vaccine
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency P1A monova-	**Proportion of children with episodes of diarrhoea caused by rotavirus G1, G2, G3, or G4 serotype , 7 months** 8/225 (4%) with high-potency G1–G4 human–bovine reassortant rotavirus vaccine 33/281 (12%) with placebo ITT analysis of participants who received 3 doses of vaccine	Vaccine efficacy 71.5% 95% CI 37.2% to 88.6% Vaccine efficacy for high-potency G1–G4 human–bovine reassortant rotavirus vaccine *v* placebo	○○○	high-potency G1–G4 human–bovine reassortant rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	lent human–bovine reassortant rotavirus vaccine				
[35] RCT **6-armed trial**	1946 healthy infants aged 2 to 8 months In review [18] Location: Finland Remaining arms: high-potency pentavalent human–bovine reassortant rotavirus vaccine; middle-potency pentavalent human–bovine reassortant rotavirus vaccine; low-potency pentavalent human–bovine reassortant rotavirus vaccine; high-potency G1–G4 human–bovine reassortant rotavirus vaccine	**Proportion of children with episodes of diarrhoea caused by rotavirus G1, G2, G3, or G4 serotype , 7 months** 22/294 (7%) with high-potency P1A monovalent human–bovine reassortant rotavirus vaccine 33/281 (12%) with placebo ITT analysis of participants who received 3 doses of vaccine	Vaccine efficacy +38.5% 95% CI –8.7% to +65.8% Vaccine efficacy for high-potency P1A monovalent human–bovine reassortant rotavirus vaccine *v* placebo	⟷	Not significant
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G1P[8] serotype , until 1 year of age** 3/9009 (0.03%) with human strain RIX4414 (2 doses) 36/8858 (0.4%) with placebo	RR 0.082 Vaccine efficacy 91.8% 95% CI 74.1% to 98.4%	●●●	human strain RIX4414
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G3P[8], G4P[8], or G9P[8] serotype , until 1 year of age** 4/9009 (0.04%) with human strain RIX4414 (2 doses) 31/8858 (0.3%) with placebo	RR 0.126 Vaccine efficacy 87.3% 95% CI 64.1% to 96.7%	●●●	human strain RIX4414
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with episodes of diarrhoea caused by G2P[4] serotype , until 1 year of age** 6/9009 (0.07%) with human strain RIX4414 (2 doses) 10/8858 (0.1%) with placebo	RR 0.59 Vaccine efficacy +41% 95% CI –79.2% to +82.4%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 serotype , 1 year** 72/2834 (3%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 286/2839 (10%) with placebo ITT analysis of participants who received at least 1 dose of vaccine	Vaccine efficacy 74.9% 95% CI 67.3% to 80.9%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus G2 serotype , 1 year** 6/2834 (0.2%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 17/2839 (0.6%) with placebo ITT analysis of participants who received at least 1 dose of vaccine	Vaccine efficacy 63.4% 95% CI 2.6% to 88.2%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus G3 serotype , 1 year** 1/2834 (0.04%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 6/2839 (0.2%) with placebo ITT analysis of participants who received at least 1 dose of vaccine	Vaccine efficacy 82.7% 95% CI <0% to 99.6%	⟷	Not significant
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus G4 serotype , 1 year** 3/2834 (0.1%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 6/2839 (0.2%) with placebo ITT analysis of participants who received at least 1 dose of vaccine	Vaccine efficacy 48.1% 95% CI <0% to 91.6%	⟷	Not significant
[31] RCT	5673 healthy infants aged 6 to 12 weeks In review [18] Location: Finland and US	**Proportion of children with episodes of diarrhoea caused by rotavirus G9 serotype , 1 year** 1/2834 (0.04%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 3/2839 (0.1%) with placebo ITT analysis of participants who received at least 1 dose of vaccine	Vaccine efficacy 65.4% 95% CI <0% to 99.3%	⟷	Not significant
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries,	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 serotype , 5.7 to 12 months**	P <0.0001 Vaccine efficacy 89.8% 95% CI 82.9% to 94.2%	○○○	10 $^{6.5}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	principally Finland (72%)	18/2572 (1%) with 10 $^{6.5}$ffu vaccine 89/1302 (7%) with placebo Per-protocol analysis			
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with episodes of diarrhoea caused by rotavirus serotype G2 , 5.7 to 12 months** 14/2572 (0.5%) with 10 $^{6.5}$ffu vaccine 17/1302 (1.3%) with placebo Per-protocol analysis	P <0.02 Vaccine efficacy 58.3% 95% CI 10.1% to 81.0%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with episodes of diarrhoea caused by rotavirus serotype G3 , 5.7 to 12 months** 3/2572 (0.1%) with 10 $^{6.5}$ffu vaccine 10/1302 (0.8%) with placebo Per-protocol analysis	P <0.002 Vaccine efficacy 84.8% 95% CI 41.0% to 97.3%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with episodes of diarrhoea caused by rotavirus serotype G4 , 5.7 to 12 months** 6/2572 (0.2%) with 10 $^{6.5}$ffu vaccine 18/1302 (1.4%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 83.1% 95% CI 55.6% to 94.5%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with episodes of diarrhoea caused by rotavirus serotype G9 , 5.7 to 12 months** 38/2572 (1%) with 10 $^{6.5}$ffu vaccine 71/1302 (5%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 72.9% 95% CI 59.3% to 82.2%	○○○	10 $^{6.5}$ffu vaccine
Proportion of children with severe episodes of diarrhoea caused by rotavirus					
[17] Systematic review	2201 healthy children aged 1.5 to 60 months 2 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 6 to 15 months** 25/1590 (2%) with human attenuated rotavirus vaccine 53/611 (9%) with placebo	RR 0.21 95% CI 0.13 to 0.35	●●○	human attenuated rotavirus vaccine
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , until 18 months of age** 0/501 (0%) with human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/639 (0%) with human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) 0/639 (0%) with human strain RIX4414 10 $^{6.1}$ffu vaccine (2 doses) 1/642 (0.2%) with placebo			
[17] Systematic review	3643 healthy children aged from newborn to 60 months 10 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 1 week to 32 months** 118/1933 (6%) with live-attenuated bovine rotavirus vaccine 218/1710 (13%) with placebo	RR 0.38 95% CI 0.24 to 0.60	●●○	live-attenuated bovine rotavirus vaccine
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients** 0/187 (0%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 8/183 (4%) with placebo	Vaccine efficacy 100% 95% CI 43.5% to 100%	○○○	quadrivalent human–bovine (WC3) reassortant rotavirus vaccine
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 7 to 9 months** 1/161 (0.6%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 4/80 (5%) with placebo Results from first and second rotavirus seasons	P = 0.016 Vaccine efficacy 90% 95% CI 36% to 99%	○○○	bovine–human rotavirus reassortant tetravalent vaccine
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 7 to 21 months** 1/161 (0.6%) with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 5/80 (6%) with placebo Results from first and second rotavirus seasons	P = 0.016 Vaccine efficacy 90% 95% CI 36% to 99%	○○○	bovine–human rotavirus reassortant tetravalent vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , until 1 year of age** 12/468 (3%) with human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses) 34/454 (7%) with placebo	P <0.001 for human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 66% 95% CI 32% to 84%	○○○	human strain RIX4414 10 $^{4.7}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Remaining arms: human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) and 10 $^{5.8}$ffu vaccine (2 doses)				
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses) and 10 $^{5.8}$ffu vaccine (2 doses)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , until 1 year of age** 102/460 (2%) with human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) 34/454 (7%) with placebo	P <0.001 for human strain RIX4414 10 $^{5.2}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 71% 95% CI 40% to 87%	○○○	human strain RIX4414 10 $^{5.2}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 10 $^{4.7}$ffu vaccine (2 doses) and 10 $^{5.2}$ffu vaccine (2 doses)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , until 1 year of age** 5/464 (1%) with human strain RIX4414 10 $^{5.8}$ffu vaccine (2 doses) 34/454 (7%) with placebo	P <0.001 for human strain RIX4414 10 $^{5.8}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 86% 95% CI 63% to 96%	○○○	human strain RIX4414 10 $^{5.8}$ffu vaccine
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , until 1 year of age** 12/9009 (0.1%) with human strain RIX4414 (2 doses) 77/8858 (0.9%) with placebo	Vaccine efficacy 84.7% 95% CI 71.7% to 92.4% RR 0.153 P <0.001	●●●	human strain RIX4414
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 18 to 22 months** 3/245 (1%) with human strain RIX4414 (2 doses) 10/123 (8%) with placebo	Vaccine efficacy 85% 95% CI 42% to 97% P = 0.001	○○○	human strain RIX4414
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , 5.7 to 12 months** 24/2572 (1%) with 10 $^{6.5}$ffu vaccine 127/1302 (10%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 90.4% 95% CI 85.1% to 94.1%	○○○	10 $^{6.5}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT	336 healthy infants aged 2 months Location: Colombia	**Proportion of children with episodes of severe diarrhoea caused by rotavirus , 2 weeks after vaccination until age 13 months** 0/159 (0%) with 10 $^{6.7}$ffu vaccine 6/160 (4%) with placebo	Vaccine efficacy 100% 95% CI 14.53% to 100% P value not reported	○○○	10 $^{6.7}$ffu vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Episodes of severe rotavirus gastroenteritis , 2 weeks after vaccination until aged 1 year** 3/100 infants/year with human rotavirus vaccine 8/100 infants/year with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Difference between groups 5/100 infants/year 95% CI 3.1/100 infants/year to 7.2/100 infants/year P value not reported	○○○	human rotavirus vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Proportion of children with episodes of severe rotavirus gastroenteritis , 2 weeks after vaccination until aged 1 year** 56/2974 (2%) with human rotavirus vaccine 70/1443 (5%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Vaccine efficacy 61.2% 95% CI 44.0% to 73.2% P <0.001	○○○	human rotavirus vaccine
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed 3 concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , age 1 year** 22/486 (5%) with pooled vaccine group (3 concentrations of human rotavirus vaccine) 19/149 (13%) with placebo 745/778 (96%) children included in per-protocol analysis 635 children in this analysis	Vaccine efficacy 64.5% 95% CI 30.7% to 81.7% P value not reported	○○○	pooled vaccine group
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , age 1 year** 9/163 (6%) with 10 $^{4.7}$ffu vaccine 19/149 (13%) with placebo 745/778 (96%) children included in per-protocol analysis	Vaccine efficacy +56.7% 95% CI –0.4% to +82.7% P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	concentrations of live-attenuated human rotavirus vaccine	319 children in this analysis			
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 9/153 (6%) with 10 $^{5.2}$ffu vaccine 19/149 (13%) with placebo 745/778 (96%) children included in per-protocol analysis 302 children in this analysis	Vaccine efficacy +53.9% 95% CI –7.0% to +81.6% P value not reported	⟷	Not significant
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil The remaining arms assessed a pooled vaccine group and 2 other concentrations of live-attenuated human rotavirus vaccine	**Proportion of children with episodes of diarrhoea of any severity caused by rotavirus , age 1 year** 4/170 (2%) with 10 $^{5.8}$ffu vaccine 19/149 (13%) with placebo 745/778 (96%) children included in per-protocol analysis 319 children in this analysis	Vaccine efficacy 81.5% 95% CI 44.5% to 95.4%	○○○	10 $^{5.8}$ffu vaccine
[26] RCT	2686 infants aged 6 to 12 weeks Location: Finland	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , up to age 2 years** 1/1088 (0.1%) with pentavalent human–bovine reassortant rotavirus vaccine (2 doses) 61/1155 (5%) with placebo Finnish cohort of REST-Europe study (30,495 children) 2243/2686 (84%) infants included in per-protocol analysis	Vaccine efficacy 98.3% 95% CI 90.2% to 100.0% P value not reported	○○○	pentavalent human–bovine reassortant rotavirus vaccine
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea caused by rotavirus , up to age 2 years** 2/5263 (0.04%) with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 51/5256 (1.00%) with placebo	P <0.001 Vaccine efficacy 96.1% 95% CI 85.1% to 99.5%	○○○	vaccine 10 $^{6.5}$ffu
[37] RCT	1312 healthy infants aged 6 to 12 weeks Location: US and Finland	**Number of infants with rotavirus gastroenteritis/days of follow-up , 1 rotavirus season** 0/78,750 with pentavalent human–bovine (WC3) vaccine (3 doses) 6/80,685 with placebo 1115/1312 (85%) children included in per-protocol analysis The RCT assessed pentavalent rotavirus vaccine "at the end of shelf life"	Vaccine efficacy 100% 95% CI 13% to 100% P value not reported	○○○	pentavalent human–bovine (WC3) vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of children with severe episodes of diarrhoea caused by rotavirus of a specific G serotype					
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) and $10^{5.8}$ffu vaccine (2 doses)	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 wild-type serotype , until 1 year of age** 7/468 (1%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 16/454 (4%) with placebo	P = 0.057 for human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy +58% 95% CI –9% to +85%	○○○	human strain RIX4414 $10^{4.7}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) and $10^{5.8}$ffu vaccine (2 doses)	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 wild-type serotype , until 1 year of age** 4/460 (1%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 16/454 (4%) with placebo	P = 0.006 for human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 75% 95% CI 24% to 94%	○○○	human strain RIX4414 $10^{5.2}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) and $10^{5.2}$ffu vaccine (2 doses)	**Proportion of children with episodes of diarrhoea caused by rotavirus G1 wild-type serotype , until 1 year of age** 2/464 (0.4%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 16/454 (4%) with placebo	P <0.001 for human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 88% 95% CI 48% to 99%	○○○	human strain RIX4414 $10^{5.8}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) and $10^{5.8}$ffu vaccine (2 doses)	**Proportion of children with episodes of diarrhoea caused by rotavirus G9 serotype , until 1 year of age** 4/468 (1%) with human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) 13/454 (3%) with placebo	P = 0.027 for human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 70% 95% CI 3% to 93%	○○○	human strain RIX4414 $10^{4.7}$ffu vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela	**Proportion of children with episodes of diarrhoea caused by rotavirus G9 serotype , until 1 year of age** 6/460 (1%) with human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) 13/454 (3%) with placebo	P = 0.109 for human strain RIX4414 $10^{5.2}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy +54% 95% CI –29% to +86%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Remaining arms: human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) and $10^{5.8}$ffu vaccine (2 doses)				
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela Remaining arms: human strain RIX4414 $10^{4.7}$ffu vaccine (2 doses) and $10^{5.2}$ffu vaccine (2 doses)	**Proportion of children with episodes of diarrhoea caused by rotavirus G9 serotype , until 1 year of age** 3/464 (0.6%) with human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) 13/454 (3%) with placebo	P = 0.011 for human strain RIX4414 $10^{5.8}$ffu vaccine (2 doses) *v* placebo Vaccine efficacy 77% 95% CI 18% to 96%	○○○	human strain RIX4414 $10^{5.8}$ffu vaccine
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus G1P[8] serotype , until 1 year of age** 3/9009 (0.03%) with human strain RIX4414 (2 doses) 32/8858 (0.4%) with placebo	Vaccine efficacy 90.8% 95% CI 70.5% to 98.2% RR 0.092	●●●	human strain RIX4414
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus G3P[8], G4P[8], or G9P[8] serotype , until 1 year of age** 4/9009 (0.04%) with human strain RIX4414 (2 doses) 30/8858 (0.3%) with placebo	Vaccine efficacy 86.9% 95% CI 62.8% to 96.6% RR 0.130	●●●	human strain RIX4414
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Proportion of children with severe episodes of diarrhoea caused by rotavirus G2P[4] serotype , until 1 year of age** 5/9009 (0.06%) with human strain RIX4414 (2 doses) 9/8858 (0.1%) with placebo	Vaccine efficacy +45.4% 95% CI –81.5% to +85.6% RR 0.55	⟷	Not significant
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G1 , 5.7 to 12 months** 4/2572 (0.2%) with $10^{6.5}$ffu vaccine 57/1302 (4%) with placebo	P <0.0001 Vaccine efficacy 96.4% 95% CI 90.4% to 99.1%	○○○	$10^{6.5}$ffu vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Per-protocol analysis			
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G2 , 5.7 to 12 months** 2/2572 (0.1%) with 10 $^{6.5}$ffu vaccine 7/1302 (0.5%) with placebo Per-protocol analysis	P <0.01 Vaccine efficacy 85.5% 95% CI 24.0% to 98.5%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G3 , 5.7 to 12 months** 1/2572 (0.04%) with 10 $^{6.5}$ffu vaccine 8/1302 (0.6%) with placebo Per-protocol analysis	P = 0.001 Vaccine efficacy 93.7% 95% CI 52.8% to 99.9%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G4 , 5.7 to 12 months** 1/2572 (0.04%) with 10 $^{6.5}$ffu vaccine 11/1302 (0.8%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 95.4% 95% CI 68.3% to 99.9%	○○○	10 $^{6.5}$ffu vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G9 , 5.7 to 12 months** 13/2572 (0.5%) with 10 $^{6.5}$ffu vaccine 44/1302 (3%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 85.0% 95% CI 71.7% to 92.6%	○○○	10 $^{6.5}$ffu vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Episodes of severe gastroenteritis caused by rotavirus serotype G1 , 2 weeks after vaccination until aged 1 year** 0.9/100 infants/year with human rotavirus vaccine 2.6/100 infants/year with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Rate difference 1.7/100 infants/year 95% CI 0.6 infants/year to 3.0/100 infants/year P value not reported	○○○	human rotavirus vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Episodes of severe gastroenteritis caused by non-G1 serotype rotavirus , 2 weeks after vaccination until aged 1 year** 2.1/100 infants/year with human rotavirus vaccine	Rate difference 3.2/100 infants/year 95% CI 1.7 infants/year to 5.1/100 infants/year P value not reported	○○○	human rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		5.3/100 infants/year with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis			
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Proportion of children with episodes of severe gastroenteritis caused by rotavirus serotype G1 , 2 weeks after vaccination until aged 1 year** 17/2974 (0.6%) with human rotavirus vaccine 23/1443 (1.6%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Vaccine efficacy 64.1% 95% CI 29.9% to 82.0% P = 0.002	○○○	human rotavirus vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Proportion of children with episodes of severe gastroenteritis caused by non-G1 serotype rotavirus , 2 weeks after vaccination until aged 1 year** 39/2974 (1%) with human rotavirus vaccine 47/1443 (3%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Vaccine efficacy 59.7% 95% CI 37.1% to 74.4% P <0.001	○○○	human rotavirus vaccine
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G1 , up to age 2 years** 0/5263 (0%) with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 21/5256 (0.4%) with placebo	P <0.001 Vaccine efficacy 100.0% 95% CI 80.8% to 100.0%	○○○	vaccine 10 $^{6.5}$ffu

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G2 , up to age 2 years** 0/5263 (0%) with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 2/5256 (0.04%) with placebo	P = 0.25 Vaccine efficacy 100% 95% CI <0% to 100%	⟷	Not significant
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G3 , up to age 2 years** 1/5263 (0.02%) with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 18/5256 (0.30%) with placebo	P <0.001 Vaccine efficacy 94.5% 95% CI 64.9% to 99.9%	○○○	vaccine 10 $^{6.5}$ffu
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Proportion of children with severe episodes of diarrhoea caused by rotavirus serotype G9 , up to age 2 years** 1/5263 (0.04%) with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 12/5256 (0.20%) with placebo	P = 0.002 Vaccine efficacy 91.7% 95% CI 43.8% to 99.8%	○○○	vaccine 10 $^{6.5}$ffu

No data from the following reference on this outcome. [25] [28]

Admissions to hospital

Compared with placebo Rotavirus vaccines seem more effective at decreasing admissions to hospital with diarrhoea (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admissions to hospital with diarrhoea from any cause					
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Admissions to hospital with diarrhoea from any cause , until 1 year of age** 145/9009 (2%) with human strain RIX4414 (2 doses) 246/8858 (3%) with placebo	Vaccine efficacy 42% 95% CI 28.6% to 53.1% RR 0.58	●○○	human strain RIX4414
[17] Systematic review	799 healthy children aged from newborn to 60 months 3 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Admissions to hospital with diarrhoea from any cause , 1 week to 32 months** 8/424 (2%) with live-attenuated bovine rotavirus vaccine 13/375 (3%) with placebo	RR 0.55 95% CI 0.16 to 1.91	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[31] RCT	68,038 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Admissions to hospital with diarrhoea from any cause , 1 year** with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) with placebo Absolute results not reported	Vaccine efficacy 59% 95% CI 52% to 65%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Admissions to hospital with diarrhoea from any cause , 5.7 to 12 months** 27/2572 (1%) with 10 $^{6.5}$focus-forming units (ffu) vaccine 48/1302 (4%) with placebo Per-protocol analysis	P <0.0001 Vaccine efficacy 71.5% 95% CI 53.4% to 82.9%	○○○	10 $^{6.5}$ffu vaccine
Admissions to hospital with diarrhoea caused by rotavirus					
[17] Systematic review	2201 healthy children aged 1.5 to 60 months 2 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Admissions to hospital with diarrhoea caused by rotavirus , 6 to 15 months** 8/1590 (1%) with human attenuated rotavirus vaccine 15/611 (2%) with placebo	RR 0.21 95% CI 0.09 to 0.48	●●○	human attenuated rotavirus vaccine
[19] [29] RCT **4-armed trial**	2155 healthy infants aged 6 to 12 weeks In review [18] Location: Brazil, Mexico, and Venezuela The 4 arms were: human strain RIX4414 10 $^{4.7}$ffu,10 $^{5.2}$ffu, and 10 $^{5.8}$ffu vaccines versus placebo	**Admissions to hospital with diarrhoea caused by rotavirus , until 1 year of age** 9/1392 (0.6%) with pooled vaccine group (human strain RIX4414 10 $^{4.7}$ffu, 10 $^{5.2}$ffu, and 10 $^{5.8}$ffu vaccines; all 2 doses) 14/454 (3%) with placebo	Pooled vaccine efficacy 79% 95% CI 48% to 92%	○○○	pooled vaccine group (human strain RIX4414 10 $^{4.7}$ffu, 10 $^{5.2}$ffu, and 10 $^{5.8}$ffu vaccines)
[32] RCT	20,169 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Admissions to hospital with diarrhoea caused by rotavirus , until 1 year of age** 9/9009 (0.1%) with human strain RIX4414 (2 doses) 59/8858 (0.7%) with placebo	Vaccine efficacy 85% 95% CI 69.6% to 93.5% RR 0.150	●●●	human strain RIX4414
[17] Systematic review	1693 healthy children aged from newborn to 60 months	**Admissions to hospital with diarrhoea caused by rotavirus , 1 week to 32 months**	RR 0.37 95% CI 0.18 to 0.74	●●○	live-attenuated bovine rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	4 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	13/962 (1%) with live-attenuated bovine rotavirus vaccine 23/731 (3%) with placebo			
[31] RCT	68,038 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Admissions to hospital with diarrhoea caused by rotavirus , 1 year** 6/28,646 (0.02%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 144/28,488 (0.50%) with placebo	Vaccine efficacy 95.8% 95% CI 90.5% to 98.2%	○○○	pentavalent human–bovine (WC3) reassortant rotavirus vaccine
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Admissions to hospital with diarrhoea caused by rotavirus , 5.7 to 12 months** with 10 $^{6.5}$ffu vaccine with placebo Absolute numbers not reported Per-protocol analysis	P <0.0001 Vaccine efficacy 83.8% 95% CI 53.4% to 99.5%	○○○	10 $^{6.5}$ffu vaccine
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Hospital admissions caused by rotavirus , 2 weeks after vaccination until aged 1 year** 14/2974 (0.5%) with human rotavirus vaccine 16/1443 (1.1%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis	Vaccine efficacy 57.5% 95% CI 7.2% to 80.8% P = 0.02	○○○	human rotavirus vaccine
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil	**Admissions to hospital with diarrhoea caused by rotavirus , age 1 year** 9/486 (1.9%) with pooled vaccine group 5/163 (3.1%) with 10 $^{4.7}$ffu vaccine 1/153 (0.7%) with 10 $^{5.2}$ffu vaccine 3/170 (1.8%) with 10 $^{5.8}$ffu vaccine 14/149 (9.4%) with placebo	Pooled vaccine efficacy 80.3% 95% CI 51.1% to 92.5% 10 $^{4.7}$ffu vaccine efficacy 67.4% 95% CI 4.1% to 90.8% 10 $^{5.2}$ffu vaccine efficacy 93.0% 95% CI 54.3% to 99.8% 10 $^{5.8}$ffu vaccine efficacy 81.2% 95% CI 32.7% to 96.5%	○○○	human rotavirus vaccine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		745/778 (96%) children included in per-protocol analysis			
[26] RCT	30,495 infants aged 6 to 12 weeks Location: Europe	**Hospital admissions caused by rotavirus , up to age 2 years** 14/14,831 (0.1%) with pentavalent human–bovine reassortant rotavirus vaccine (2 doses) 172/14,734 (1.2%) with placebo	Rate reduction 91.9% 95% CI 86.0% to 95.6% P value not reported	○○○	pentavalent human–bovine reassortant rotavirus vaccine
[28] RCT	2066 premature infants (up to 36 weeks' gestation) Further report of reference [32] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Hospital admissions caused by rotavirus , 1 week to 32 months** 0/938 (0%) with pentavalent human–bovine vaccine (WC3) (3 doses) 10/990 (1%) with placebo Infants were considered eligible if thriving at the time of enrolment	Rate reduction 100% 95% CI 58.8% to 100% P value not reported	○○○	pentavalent human–bovine vaccine

No data from the following reference on this outcome. [20] [22] [25] [27] [34] [35] [36] [37] [38]

Mortality

Compared with placebo Rotavirus vaccines may be no more effective at decreasing mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[32] RCT	63,225 healthy infants aged 6 to 13 weeks In review [18]	**Mortality , until 1 year of age** 56/31,673 (0.2%) with human strain RIX4414 (2 doses) 43/31,552 (0.1%) with placebo	RR 1.30 95% CI 0.87 to 1.93 P = 0.20	⟷	Not significant
[31] RCT	68,038 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Mortality , 1 year** 24/34,035 (0.07%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 20/34,003 (0.06%) with placebo	Significance not assessed		
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Mortality , 2 weeks after vaccination until aged 1 year** 83/3298 (2.5%) with human rotavirus vaccine 43/1641 (2.6%) with placebo Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis; 99.9% of infants included in safety analysis			
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Mortality , up to age 2 years** 1/5263 with human attenuated rotavirus vaccine 10 $^{6.5}$ focus-forming units (ffu) 3/5256 with placebo All deaths were considered unrelated to vaccination	P = 0.3	⟷	Not significant
[28] RCT	2066 premature infants (up to 36 weeks' gestation) Further report of reference [32] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Mortality , 1 week to 32 months** with pentavalent human–bovine vaccine (WC3) (3 doses) with placebo 2 deaths were reported in each group; none of the deaths was considered vaccine related Infants were considered eligible if thriving at the time of enrolment			
[37] RCT	1312 healthy infants aged 6 to 12 weeks Location: US and Finland	**Mortality , 1 rotavirus season** 1/650 with pentavalent human–bovine (WC3) vaccine (3 doses) 0/660 with placebo The death in the vaccine group was assessed as unrelated to vaccine The RCT assessed pentavalent rotavirus vaccine "at the end of shelf life"	Significance not assessed		

No data from the following reference on this outcome. [17] [19] [20] [21] [22] [24] [25] [26] [29] [32] [34] [35] [36] [38]

Life-threatening adverse events

Compared with placebo Rotavirus vaccines may lead to fewer life-threatening adverse events than placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Serious adverse events					
[32] RCT	63,225 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua,	**Serious adverse events , until 1 year of age** 928/31,673 (2.9%) with human strain RIX4414 (2 doses) 1047/31,552 (3.3%) with placebo Serious adverse events defined as any untoward medical occurrence that resulted in death, was life-threatening, required admission to hospital, prolonged exist-	RR 0.88 95% CI 0.81 to 0.96 P = 0.005	●○○	human strain RIX4414

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Panama, Peru, and Venezuela	ing hospital stay, or resulted in disability or incapacity			

No data from the following reference on this outcome. [17] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [31] [34] [35] [36] [37] [38]

Adverse events requiring admission to hospital

Compared with placebo Rotavirus vaccines seem to lead to fewer adverse events requiring admission to hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse events leading to admission to hospital					
[32] RCT	63,225 healthy infants aged 6 to 13 weeks In review [18] Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela	**Hospital admission , until 1 year of age** 886/31,673 (2.8%) with human strain RIX4414 (2 doses) 1003/31,552 (3.2%) with placebo	RR 0.88 95% CI 0.81 to 0.96 P = 0.005	●○○	human strain RIX4414

No data from the following reference on this outcome. [17] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [31] [34] [35] [36] [37] [38]

Intussusception

Compared with placebo Rotavirus vaccines do not seem associated with an increased risk of intussusception (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Intussusception					
[32] RCT	63,225 healthy infants aged 6 to 13 weeks In review [18]	**Intussusception , until 1 year of age** 9/31,673 (0.03%) with human strain RIX4414 (2 doses) 16/31,552 (0.05%) with placebo	RR 0.56 95% CI 0.25 to 1.24 P = 0.16	⟷	Not significant
[31] RCT	68,038 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Intussusception , 1 year** 12/34,035 (0.04%) with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 15/34,003 (0.04%) with placebo	RR 0.8 95% CI 0.3 to 1.8	⟷	Not significant
[27] RCT	10,708 healthy infants aged 6 to 17 weeks	**Intussusception , up to age 2 years**	P = 0.25	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Location: Hong Kong, Singapore, and Taiwan	8/5263 (0.2%) with human attenuated rotavirus vaccine 10 $^{6.5}$ focus-forming units (ffu) 4/5256 (0.1%) with placebo No cases of intussusception were reported in the 31 days after vaccination			

No data from the following reference on this outcome. [17] [19] [20] [21] [22] [23] [24] [25] [26] [28] [29] [34] [35] [36] [37] [38]

Gastrointestinal adverse effects

Compared with placebo Rotavirus vaccines do not seem associated with an increased risk of gastrointestinal adverse effects (vomiting, diarrhoea, blood in stools, loss of appetite) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[17] Systematic review	331 healthy children aged 1.5 to 60 months 2 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Vomiting , 1 week after receipt of vaccine or placebo** 24/169 (14%) with human attenuated rotavirus vaccine 12/162 (7%) with placebo	RR 1.94 95% CI 1.00 to 3.75	⟷	Not significant
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Vomiting , 15 days after receipt of the first dose of vaccine or placebo** 9/265 (3%) with human strain RIX4414 (2 doses) 5/133 (4%) with placebo	Significance not assessed		
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Vomiting , 15 days after receipt of the first dose of vaccine or placebo** 5/510 (1.0%) with human strain RIX4414 10 $^{4.7}$ focus-forming units (ffu) vaccine (2 doses) 5/648 (0.8%) with human strain RIX4414 10 $^{5.2}$ ffu vaccine (2 doses) 7/653 (1.1%) with human strain RIX4414 10 $^{6.1}$ ffu vaccine (2 doses) 6/653 (0.9%) with placebo	Significance not assessed		
[17] Systematic review	2016 healthy children aged from newborn to 60 months 10 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Re-	**Vomiting , 5 days to 4 weeks after receipt of vaccine or placebo** 262/1109 (24%) with live-attenuated bovine rotavirus vaccine 202/907 (22%) with placebo	RR 1.05 95% CI 0.90 to 1.22	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	public, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US				
[31] RCT	9605 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Vomiting , 42 days after receipt of any dose of vaccine or placebo** 13% with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 13% with placebo Absolute numbers not reported	Significance not assessed		
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Vomiting , 14 days after receipt of any dose of vaccine or placebo** 58/218 (27%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 52/220 (24%) with placebo	ARI +3% 95% CI –5.9% to +12%	⟷	Not significant
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Vomiting , 7 days after receipt of the first dose of vaccine or placebo** 11.8% with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 20.5% with placebo Absolute numbers not reported	P = 0.04	○○○	bovine–human rotavirus reassortant tetravalent vaccine
Diarrhoea					
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Diarrhoea , 15 days after receipt of the first dose of vaccine or placebo** 8/265 (3%) with human strain RIX4414 (2 doses) 5/133 (4%) with placebo	Significance not assessed		
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Diarrhoea , 15 days after receipt of the first dose of vaccine or placebo** 1/510 (0.2%) with human strain RIX4414 $10^{4.7}$ ffu vaccine (2 doses) 1/648 (0.2%) with human strain RIX4414 $10^{5.2}$ ffu vaccine (2 doses) 3/653 (0.5%) with human strain RIX4414 $10^{6.1}$ ffu vaccine (2 doses) 2/653 (0.3%) with placebo	Significance not assessed		
[31] RCT	9605 healthy infants aged 6 to 12 weeks	**Diarrhoea , 42 days after receipt of any dose of vaccine or placebo**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	20% with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 19% with placebo Absolute numbers not reported			
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Diarrhoea , 14 days after receipt of any dose of vaccine or placebo** 97/218 (45%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 80/220 (36%) with placebo	ARI +8.1% 95% CI –1.5% to +17.8%	⟷	Not significant
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Diarrhoea , 7 days after receipt of the first dose of vaccine or placebo** 7.1% with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 7.2% with placebo Absolute numbers not reported	P = 1.00	⟷	Not significant
[31] RCT	9605 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Blood in the stools , 42 days after receipt of any dose of vaccine or placebo** 0.6% with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 0.6% with placebo Absolute numbers not reported	Significance not assessed		
Loss of appetite					
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Loss of appetite , 15 days after receipt of the first dose of vaccine or placebo** 24/265 (9%) with human strain RIX4414 (2 doses) 17/133 (13%) with placebo	Significance not assessed		
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Loss of appetite , 7 days after receipt of the first dose of vaccine or placebo** 7.5% with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 6.4% with placebo Absolute numbers not reported	P = 0.83	⟷	Not significant

No data from the following reference on this outcome. [19] [21] [22] [23] [24] [25] [26] [27] [28] [29] [32] [35] [37]

Fever

Compared with placebo Rotavirus vaccines are not associated with an increased risk of fever (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fever					
[17] Systematic review	716 healthy children aged 1.5 to 60 months 5 RCTs in this analysis Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs US; and 1 RCT Venezuela	**Fever , 1 week after receipt of vaccine or placebo** 24/169 (14%) with human attenuated rotavirus vaccine 12/162 (7%) with placebo	RR 1.94 95% CI 1.00 to 3.75	⟷	Not significant
[34] RCT **4-armed trial**	2464 healthy infants aged 11 to 17 weeks In review [18] Location: Singapore	**Fever , 15 days after receipt of the first dose of vaccine or placebo** 30/510 (5.9%) with human strain RIX4414 $10^{4.7}$ focus-forming units (ffu) vaccine (2 doses) 28/648 (4.3%) with human strain RIX4414 $10^{5.2}$ ffu vaccine (2 doses) 25/653 (3.8%) with human strain RIX4414 $10^{6.1}$ ffu vaccine (2 doses) 28/653 (4.3%) with placebo	Significance not assessed		
[36] RCT	405 healthy infants aged 6 to 12 weeks In review [18] Location: Finland	**Fever , 15 days after receipt of the first dose of vaccine or placebo** 12/265 (5%) with human strain RIX4414 (2 doses) 11/133 (8%) with placebo	Significance not assessed		
[17] Systematic review	2168 healthy children aged from newborn to 60 months 12 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Fever , 5 days to 4 weeks after receipt of vaccine or placebo** 140/1182 (11.8%) with live-attenuated bovine rotavirus vaccine 118/986 (12.0%) with placebo	RR 0.95 95% CI 0.73 to 1.23	⟷	Not significant
[31] RCT	9605 healthy infants aged 6 to 12 weeks In review [18] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Fever , 42 days after receipt of any dose of vaccine or placebo** 41% with pentavalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 43% with placebo Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Fever , 14 days after receipt of any dose of vaccine or placebo** 70/218 (32%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 73/220 (33%) with placebo	ARI –1.1% 95% CI –10.9% to +8.0%	⟷	Not significant
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Fever , 7 days after receipt of the first dose of vaccine or placebo** 16.1% with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 12.3% with placebo Absolute numbers not reported	P = 0.42	⟷	Not significant
[38] RCT	258 healthy infants aged 50 to 122 days In review [18] Location: Finland	**Antipyretic use , 7 days after receipt of the first dose of vaccine or placebo** 6.9% with bovine–human rotavirus reassortant tetravalent vaccine (2 doses) 5.1% with placebo Absolute numbers not reported	P = 0.64	⟷	Not significant

No data from the following reference on this outcome. [19] [21] [22] [23] [24] [25] [26] [27] [28] [29] [32] [35] [37]

Irritability

Compared with placebo We don't know whether rotavirus vaccines are more effective at reducing irritability at 1 to 4 weeks after administration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Irritability					
[17] Systematic review	215 healthy children aged 1.5 to 60 months Data from 1 RCT Location: US	**Irritability , 1 week after receipt of vaccine or placebo** 37/108 (34%) with human attenuated rotavirus vaccine 52/107 (49%) with placebo	RR 0.70 95% CI 0.51 to 0.98	●○○	human attenuated rotavirus vaccine
[17] Systematic review **3-armed trial**	512 healthy children aged from newborn to 60 months 10 RCTs in this analysis Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs US	**Irritability , 5 days to 4 weeks after receipt of vaccine or placebo** 95/255 (37%) with live-attenuated bovine rotavirus vaccine 89/257 (35%) with placebo	RR 1.08 95% CI 0.86 to 1.36	⟷	Not significant
[36] RCT	405 healthy infants aged 6 to 12 weeks	**Irritability , 15 days after receipt of the first dose of vaccine or placebo**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [18] Location: Finland	62/265 (23%) with human strain RIX4414 (2 doses) 60/133 (45%) with placebo			
[20] RCT	439 healthy infants aged 2 to 6 months Location: US	**Irritability , 14 days after receipt of any dose of vaccine or placebo** 86/218 (39%) with quadrivalent human–bovine (WC3) reassortant rotavirus vaccine (3 doses) 93/220 (42%) with placebo	ARI –2.8% 95% CI –12.8% to +6.5%	⟷	Not significant

No data from the following reference on this outcome. [19] [21] [22] [23] [24] [25] [26] [27] [28] [29] [31] [32] [34] [35] [37] [38]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment-related adverse effects					
[24] RCT **4-armed trial**	778 healthy infants aged 6 to 12 weeks Location: Brazil	**Proportion of children with at least 1 adverse event , within 43 days following any vaccination** 78.9% with $10^{4.7}$ focus-forming units (ffu) vaccine 78.6% with $10^{5.2}$ ffu vaccine 75.3% with $10^{5.8}$ ffu vaccine 78.9% with placebo Absolute numbers not reported 745/778 (96%) children included in per-protocol analysis	Significance not assessed		
[25] RCT	189 healthy infants aged 6 to 12 weeks Location: Taiwan	**Treatment-related adverse effects , within 42 days following any vaccination** with pentavalent human–bovine reassortant vaccine (2 doses) with placebo The RCT reported no significant differences between vaccine- and placebo-treated infants in treatment-related fever, diarrhoea, vomiting, or irritable crying The RCT reported no cases of intussusception in either group	P value for total adverse effects not reported	⟷	Not significant
[26] RCT	2686 infants aged 6 to 12 weeks Location: Finland	**Proportion of infants with at least 1 systemic adverse event , within 7 days following first dose** 131/1343 (9.8%) with pentavalent human–bovine reassortant rotavirus vaccine (2 doses) 125/1341 (9.3%) with placebo Finnish cohort of REST-Europe study (30,495 children)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCT report no cases of intussusception in either group			
Serious adverse events					
[21] RCT	3994 healthy infants aged 6 to 14 weeks Location: 6 European countries, principally Finland (72%)	**Serious adverse effects , 5.7 to 12 months** 290/2646 (11%) with 10 $^{6.5}$ffu vaccine 176/1348 (13%) with placebo The RCT reported 1 case of intussusception 8 days after second vaccine dose Per-protocol analysis	Significance not assessed		
[23] RCT **3-armed trial**	4939 infants aged 5 to 10 weeks including infants with HIV infection Location: South Africa and Malawi	**Proportion of children with at least 1 serious adverse event , 2 weeks after vaccination until aged 1 year** 319/3298 (10%) with human rotavirus vaccine 189/1641 (12%) with placebo 1 case of intussusception occurred 11 weeks after the third dose of vaccine in a 6-month-old child Study design included 3 arms (3 doses of vaccine; 2 doses of vaccine plus 1 dose placebo; 3 doses placebo), but it also reported results for the pooled vaccine groups versus placebo. We report those results here, as effectively a 2-arm trial Per-protocol analysis: >89% of infants included in efficacy analysis; 99.9% of infants included in safety analysis	Significance not assessed		
[27] RCT	10,708 healthy infants aged 6 to 17 weeks Location: Hong Kong, Singapore, and Taiwan	**Serious adverse events , up to age 2 years** 1868 per 10,000 children with human attenuated rotavirus vaccine 10 $^{6.5}$ffu 2053 per 10,000 children with placebo	P = 0.016	○○○	vaccine 10 $^{6.5}$ffu
[28] RCT	2066 premature infants (up to 36 weeks' gestation) Further report of reference [32] Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and US	**Proportion of children with at least 1 serious adverse event within 42 days of any dose , 1 week to 32 months** 55/1005 (5.5%) with pentavalent human–bovine vaccine (WC3) (3 doses) 62/1061 (5.8%) with placebo Infants were considered eligible if thriving at the time of enrolment No cases of intussusception were reported	Significance not assessed		
[37] RCT	1312 healthy infants aged 6 to 12 weeks	**Proportion of children with serious adverse events , 1 rotavirus season**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Location: US and Finland	21/650 (3%) with pentavalent human–bovine (WC3) vaccine (3 doses) 27/660 (4%) with placebo The RCT assessed pentavalent rotavirus vaccine "at the end of shelf life"			

No data from the following reference on this outcome. [17] [18] [19] [20] [22] [29] [31] [34] [35] [36] [38]

Further information on studies

[17] Of the 64 RCTs evaluated in the systematic review, 49 did not report information about the generation of the allocation sequence, three RCTs did not provide information on blinding, and 6 RCTs did not provide information on withdrawals before study end. The authors of the review noted statistical heterogeneity among RCTs for many of the outcomes assessed (P <0.10 for the outcome of episodes of diarrhoea [either caused by rotavirus or all-cause]; statistical heterogeneity set by review as significant if P <0.10). The authors of the review suggest that the wide variation in protection across the individual RCTs may be related to the study design, study population, or the response of the immune system to different strains of rotavirus or rotavirus vaccine. The systematic review gave no information on the incidence of intussusception or death from any cause for either the human attenuated rotavirus vaccine or live-attenuated bovine rotavirus vaccine.

[19] [29] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay, and the percentage of stools that were not analysed was 26%. Rates of fever, diarrhoea, vomiting, irritability, loss of appetite, and cough/runny nose were similar among groups at 15 days after receipt of any dose of human strain RIX4414 (10 $^{4.7}$ffu, 10 $^{5.2}$ffu, or 10 $^{5.8}$ffu; all 2 doses) or placebo (data presented graphically, significance not assessed). Three deaths were reported; no other details provided.

[31] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay; however, the percentage of stools that were analysed was not reported.

[32] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay; however, the percentage of stools that were analysed was not reported.

[36] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay, and the percentage of stools that were not analysed was 7%. This RCT randomly allocated children at a vaccine-to-placebo ratio of 2:1. No cases of intussusception were reported in either the human strain RIX4414 or placebo groups (significance not assessed).

[34] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay, and the percentage of stools that were not analysed was 41%. Serious adverse effects (those that prevent normal daily activity) were deemed to be possibly related to vaccination in 4 children receiving either human strain RIX4414 (10 $^{4.7}$ffu, 10 $^{5.2}$ffu, or 10 $^{6.1}$ffu; all 2 doses) or placebo, including 1 case of intussusception in a boy who received 10 $^{5.2}$ffu vaccine (significance was not assessed). Three deaths were reported in this RCT: two deaths in the human strain RIX4414 10 $^{6.1}$ffu group and one in the human strain RIX4414 10 $^{5.2}$ffu group (significance not assessed).

[20] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay; however, the percentage of stools that were analysed was not reported.

[38] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay; however, the percentage of stools that were analysed was not reported. This RCT randomly allocated children at a vaccine-to-placebo ratio of 2:1.

[35] Stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay. In this RCT, 23% of children were excluded from the per-protocol analysis because they were not evaluable with regard to the case definition for rotavirus gastroenteritis. The RCT had an uneven distribution of children in each group because of a short supply of one of the vaccines. Similar rates of fever were reported among the groups (high-potency pentavalent vaccine, middle-potency pentavalent vaccine, low-potency pentavalent vaccine, high-potency G1–G4 vaccine, high-potency P1A monovalent vaccine [all human–bovine reassortant rotavirus vaccines, administered at 3 doses each], and placebo); data presented graphically, significance not assessed.

One case of intussusception was reported in the low-potency pentavalent vaccine group. No deaths were reported in this RCT (significance not assessed).

Comment: The case definitions and scoring systems for severe gastroenteritis differed between RCTs, and the criteria for admission to hospital was likely to have varied between centres and countries; these factors make the comparison between vaccines difficult. The percentage of stools analysed also varied between RCTs, although several studies did not report this information. In one RCT, participants whose stool specimens were not analysed were excluded from the analysis, [35] thus increasing the likelihood of bias and reducing the quality of the RCT. Monitoring for intussusception in infants in developing communities is ongoing after the market introduction of rotavirus vaccine.

Clinical guide:
Currently licensed rotavirus vaccines decrease the number of rotavirus gastroenteritis episodes, the severity of diarrhoea caused by rotavirus, and the need for admissions to hospital. Large safety studies have shown no increased risk of adverse events, including intussusception. Given that rotavirus is a major cause of severe diarrhoeal illness worldwide, rotavirus vaccination would be equally beneficial for developed and developing communities. Rotavirus vaccination is part of the routine vaccination schedule in several countries, including the US and Australia.

QUESTION What are the effects of treatments for acute gastroenteritis in children?

OPTION ENTERAL REHYDRATION SOLUTIONS

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Enteral rehydration solutions containing sugar or food plus electrolytes are as effective as intravenous fluids at correcting dehydration and reducing the duration of hospital stay, and may have fewer major adverse effects.

Benefits and harms

Enteral rehydration versus intravenous rehydration:

We found three systematic reviews. [39] [40] [41] Of these, we report results from the two with the most relevant outcomes (search date 2003 [39] and search date 2006, including children up to 18 years of age with acute gastroenteritis [40]). The third review [41] focused on the outcome of treatment failure, which is defined variably in different studies, and can be difficult to define with intravenous therapy.

Duration of diarrhoea

Enteral rehydration compared with intravenous rehydration We don't know whether enteral rehydration is more effective than intravenous rehydration at reducing the duration of diarrhoea or at promoting weight gain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of diarrhoea					
[39] Systematic review	946 children 8 RCTs in this analysis	**Duration of diarrhoea** with enteral rehydration with intravenous rehydration Absolute results not reported	WMD –6.39 hours 95% CI –13.73 hours to +0.94 hours	⟷	Not significant
[39] Systematic review	494 children 2 RCTs in this analysis Subgroup analysis	**Duration of diarrhoea** with nasogastric rehydration with intravenous rehydration Absolute results not reported	WMD –17.77 hours 95% CI –27.55 hours to –7.99 hours	○○○	nasogastric rehydration
[39] Systematic review	415 children 5 RCTs in this analysis Subgroup analysis	**Duration of diarrhoea** with oral rehydration with intravenous rehydration Absolute results not reported	WMD +1.76 hours 95% CI –0.91 hours to +4.42 hours	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[40] Systematic review	960 children up to 18 years of age with acute gas-troenteritis 8 RCTs in this analysis	**Duration of diarrhoea** with oral rehydration with intravenous rehydration Absolute results not reported	WMD –5.90 hours 95% CI –12.70 hours to +0.89 hours	⟷	Not significant

Duration of hospital stay

Enteral rehydration compared with intravenous rehydration Enteral rehydration may be more effective than intravenous rehydration at reducing the duration of hospital stay (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of hospital stay					
[39] Systematic review	161 children 3 RCTs in this analysis	**Duration of hospital stay** with enteral rehydration with intravenous rehydration Absolute results not reported	WMD –0.88 days 95% CI –1.45 days to –0.32 days	○○○	enteral rehydration
[40] Systematic review	526 children up to 18 years of age with acute gas-troenteritis 6 RCTs in this analysis	**Duration of hospital stay** with oral rehydration with intravenous rehydration Absolute results not reported	WMD –1.2 days 95% CI –2.38 days to –0.02 days	○○○	oral rehydration

Admissions to hospital

No data from the following reference on this outcome. [39] [40]

Weight gain

Enteral rehydration compared with intravenous rehydration We don't know whether enteral rehydration is more effective than intravenous rehydration at improving weight gain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Weight gain					
[39] Systematic review	276 children 5 RCTs in this analysis	**Weight gain** with enteral rehydration with intravenous rehydration Absolute results not reported	WMD –26 g 95% CI –60.8 g to +9.7 g	⟷	Not significant
[40] Systematic review	526 children up to 18 years of age with acute gas-troenteritis 6 RCTs in this analysis	**Weight gain** with oral rehydration with intravenous rehydration Absolute results not reported	WMD –26.33 g 95% CI –206.92 g to +154.26 g	⟷	Not significant

Total stool volume

No data from the following reference on this outcome. [39] [40]

Mortality

No data from the following reference on this outcome. [39] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Major adverse effects					
[39] Systematic review	1545 children 16 RCTs in this analysis	**Death or seizure as a result of treatment** 5/886 (1%) with enteral rehydration 15/659 (2%) with intravenous rehydration Absolute results not reported	RR 0.36 95% CI 0.14 to 0.89	●●○	enteral rehydration

Further information on studies

[39] Results for weight gain excluded one RCT in a population of under-nourished children; inclusion of this study in meta-analyses resulted in significant heterogeneity. Analysis of major adverse events (death or seizure) was strongly weighted by one large RCT conducted in a developing community in 1985 in children with severe gastroenteritis, exclusion of which rendered the results not significant. The review did not report on minor adverse events. The RCTs included in the review were of variable quality, and many did not report sufficient information about randomisation, blinding, and allocation concealment to enable quality assessment of included trials. RCTs included children with a wide age range, with variable degrees of dehydration, and with different socioeconomic backgrounds; they also included RCTs with different modes of oral therapy (by mouth or nasogastric tube).

[40] The review found that only three of the 17 trials reported deaths, with all reported deaths occurring in low- to middle-income countries. They found that phlebitis was more common in those given intravenous rehydration (NNT 50, 95% CI 25 to 100). Paralytic ileus was more common in those treated with oral rehydration (NNT 33, 95% CI 20 to 100). The RCTs included in the systematic review were of variable quality, and many did not report sufficient information about randomisation, blinding, and allocation concealment to enable quality assessment of included trials. RCTs included children with a wide age range, with variable degrees of dehydration, and with different socioeconomic backgrounds; they also included RCTs with different modes of oral therapy (by mouth or nasogastric tube).

Comment: **Clinical guide:**
There is evidence from systematic reviews that enteral and intravenous rehydration are equally effective for the management of mild to moderate dehydration. It is accepted practice in developed communities that children who are shocked or severely dehydrated require intravenous fluids.

OPTION LACTOSE-FREE FEEDS

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Lactose-free feeds may reduce the duration of diarrhoea in children with mild to severe dehydration compared with feeds containing lactose, but studies have shown conflicting results.

Benefits and harms

Lactose-free feeds versus feeds containing lactose:

We found one systematic review (search date not reported) [42] and 5 subsequent RCTs [43] [44] [45] [46] [47] comparing feeds containing lactose versus lactose-free feeds.

Duration of diarrhoea

Compared with feeds containing lactose Lactose-free feeds may be more effective at reducing the duration of diarrhoea and stool frequency in children with mild to severe dehydration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of diarrhoea					
[42] Systematic review	826 children with mild or no dehydration receiving oral rehydration treatment 9 RCTs in this analysis	**Mean duration of diarrhoea** 92 hours with feeds containing lactose 88 hours with lactose-free feeds	Reported as significant P value not reported	○○○	lactose-free feeds
[42] Systematic review	604 children with mild or no dehydration receiving oral rehydration treatment 6 RCTs in this analysis Subgroup analysis Subgroup excluding the 3 RCTs that included children given additional solid food	**Mean duration of diarrhoea** 95 hours with feeds containing lactose 82 hours with lactose-free feeds	Reported as significant P value not reported	○○○	lactose-free feeds
[43] RCT	76 children with acute diarrhoea and mild to moderate dehydration aged 2 to 12 months	**Duration of diarrhoea** 6.6 days with cows' milk 4.5 days with soy-based formula	P <0.01	○○○	soy-based formula
[44] RCT	60 children with acute diarrhoea aged <1 year	**Duration of diarrhoea** with formula containing lactose with lactose-free formula Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[45] RCT	52 children with acute diarrhoea and mild to moderate dehydration aged 1 to 24 months	**Duration of diarrhoea** with formula containing lactose with lactose-free formula Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[46] RCT	200 boys with acute diarrhoea aged 3 to 18 months	**Duration of diarrhoea** 39 hours with soy-based formula with lactose 23 hours with soy-based formula with sucrose	P <0.001	○○○	soy-based formula with sucrose
[47] RCT **3-armed trial**	91 children with acute gastroenteritis aged <24 months The other arm was formula containing	**Duration of diarrhoea** 38 hours with formula containing lactose 25 hours with lactose-free formula	P <0.03	○○○	lactose-free formula

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	low levels of lactose				

Duration of hospital stay

No data from the following reference on this outcome. [42] [43] [44] [45] [46] [47]

Admissions to hospital

No data from the following reference on this outcome. [42] [43] [44] [45] [46] [47]

Weight gain

Compared with feeds containing lactose We don't know whether lactose-free feeds are more effective at improving weight gain (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Weight gain					
[43] RCT	76 children with acute diarrhoea and mild to moderate dehydration aged 2 to 12 months	**Weight gain** with cows' milk with soy-based formula Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[44] RCT	60 children with acute diarrhoea aged <1 year	**Weight gain** with formula containing lactose with lactose-free formula Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[45] RCT	52 children with acute diarrhoea and mild to moderate dehydration aged 1 to 24 months	**Weight gain** with formula containing lactose with lactose-free formula Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[46] RCT	200 boys with acute diarrhoea aged 3 to 18 months	**Weight gain** with soy-based formula with lactose with soy-based formula with sucrose Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[47] RCT **3-armed trial**	91 children with acute gastroenteritis aged <24 months The other arm was formula containing low levels of lactose	**Weight gain** 7.48 kg with formula containing lactose 7.84 kg with lactose-free formula	P <0.05	○○○	lactose-free formula

No data from the following reference on this outcome. [42]

Total stool volume

Compared with feeds containing lactose Lactose-free feeds may be more effective at reducing total stool volume (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total stool volume					
[42] Systematic review	209 children with mild or no dehydration receiving oral rehydration treatment 4 RCTs in this analysis	**Total stool volume** with feeds containing lactose with lactose-free feeds	P = 0.002	○○○	lactose-free feeds
[46] RCT	200 boys with acute diarrhoea aged 3 to 18 months	**Mean total stool volume (mL/kg body weight)** 164 mL/kg (95% CI 131 mL/kg to 208 mL/kg) with soy-based formula with lactose 69 mL/kg (95% CI 55 mL/kg to 87 mL/kg) with soy-based formula with sucrose	P <0.001	○○○	soy-based formula with sucrose

No data from the following reference on this outcome. [43] [44] [45] [47]

Mortality

No data from the following reference on this outcome. [42] [43] [44] [45] [46] [47]

Adverse effects

No data from the following reference on this outcome. [42] [43] [44] [45] [46] [47]

Further information on studies

[42] The review found that feeds containing lactose significantly increased "treatment failure" compared with lactose-free feeds (13 RCTs, 873 children with mild to severe dehydration; treatment failure rate: 89/399 [22%] with lactose *v* 56/474 [12%] with lactose-free feeds; RR 2.1, 95% CI 1.6 to 2.7). However, the definition of treatment failure varied among trials, and included increasing severity or persistence of diarrhoea or recurrence of dehydration. Differences in weight gain during treatment could not be assessed by the systematic review, because of the use of solid food in two studies and considerable heterogeneity among studies. Although the systematic review stated criteria for inclusion and exclusion of RCTs, only published studies were included, and the method of determining RCT quality was not reported. There was considerable heterogeneity among studies, which limits the validity of the meta-analyses. Lactose-free feeds were superior to feeds containing lactose for decreasing the duration of diarrhoea. Differences for other outcomes, although statistically significant, were not clinically important.

[43] The RCT found no significant difference between cows' milk and soy-based formula in treatment failure; no further details provided.

[45] The RCT found no significant difference between formula containing lactose and lactose-free formula in treatment failure; no further details provided. This RCT was the only RCT to assess adverse effects, and it reported no adverse effects in the treatment or control groups.

[46] The RCT found no significant difference between soy-based formula with lactose and soy-based formula with sucrose in treatment failure; no further details provided.

Comment: A protocol on "Lactose avoidance for acute diarrhoea in children less than five years" has been published in The Cochrane Library. [48]

Clinical guide:
There is evidence that lactose-free feeds can decrease the duration of diarrhoea compared with lactose-containing feeds, but the existing systematic review is limited by weaknesses in the methods used. Routine use of lactose-free feeds is currently not recommended. We await the results of the Cochrane Review that is under way.

OPTION LOPERAMIDE

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Loperamide can reduce the prevalence of acute diarrhoea in children in the first 48 hours after initiation of treatment, but there is an increased risk of adverse effects compared with placebo.

Benefits and harms

Loperamide versus placebo:

We found one systematic review (search date 2006, 13 RCTs, 1788 children) [49] comparing loperamide versus placebo.

Duration of diarrhoea

Compared with placebo Loperamide may be more effective at reducing the duration of diarrhoea in children, but we are not certain, as results were sensitive to the method of analysis used (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of diarrhoea					
[49] Systematic review	976 children 6 RCTs in this analysis	**Mean duration of diarrhoea** with loperamide with placebo Absolute results not reported	Mean reduction 0.8 days 95% CI 0.7 days to 0.9 days	○○○	loperamide
[49] Systematic review	Number of children not reported Subgroup analysis Subanalysis of the RCTs that satisfied all 4 indicators of quality (generation of allocation sequence, allocation concealment, double-blind RCT, and >90% of children randomised to treatment). Number of trials in analysis not reported	**Mean duration of diarrhoea** with loperamide with placebo Absolute results not reported	Mean difference –0.67 days 95% CI –1.35 days to +0.01 days	⟷	Not significant

Duration of hospital stay

No data from the following reference on this outcome. [49]

Admissions to hospital

No data from the following reference on this outcome. [49]

Weight gain

No data from the following reference on this outcome. [49]

Total stool volume

No data from the following reference on this outcome. [49]

Mortality

No data from the following reference on this outcome. [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[49] Systematic review	1691 children 12 RCTs in this analysis	**Adverse effects** 94/927 (10%) with loperamide 16/764 (2%) with placebo	ARI 8.6% 95% CI 6.4% to 10.9%	○○○	placebo
[49] Systematic review	1691 children 12 RCTs in this analysis	**Serious adverse effects (defined as ileus, lethargy, or death)** 8/927 (1%) with loperamide 0/764 (0%) with placebo	ARI +0.8% 95% CI –0.1% to +1.8%	⟷	Not significant
[49] Systematic review	1691 children 12 RCTs in this analysis	**Serious adverse effects (defined as ileus, lethargy, death abdominal distension, and sleepiness)** 21/927 (2%) with loperamide 4/764 (1%) with placebo	ARI 1.8% 95% CI 0.6% to 3.1%	○○○	placebo

Further information on studies

[49] The review did not pool data for stool volume or admission to hospital because there were insufficient data for analysis reported in the identified RCTs. The authors of the review reported statistical heterogeneity among RCTs for the outcome of duration of diarrhoea (P <0.01); subgroup analyses did not identify the source of heterogeneity. The systematic review included open-label studies (4 RCTs), and reported that some of the RCTs did not report generation of allocation sequence (6 RCTs) or allocation concealment (6 RCTs). Serious adverse effects occurred only in children under 3 years of age. One death occurred in a child taking loperamide caused by *Salmonella typhi* bacteraemia.

Comment: The quality of some of the studies included in the systematic review was poor because of lack of allocation-concealment reporting and non-blinding. These factors may have resulted in bias in favour of the intervention compared with placebo.

Clinical guide:
Although loperamide reduces the persistence of acute diarrhoea in children, it is not recommended for children under 3 years of age because the risk of adverse effects outweighs the benefits in this group.

OPTION ONDANSETRON

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Ondansetron reduces vomiting but increases diarrhoea in children with gastroenteritis, compared with placebo.

Benefits and harms

Ondansetron versus placebo:

We found three systematic reviews (search date 2008, 4 RCTs, 501 children; [50] search date 2007; [51] and search date 2006, 4 RCTs, 490 children [52]) and one subsequent RCT [53] comparing ondansetron with placebo. The second systematic review [51] included in its meta-analyses an RCT that included people aged up to 22 years, and so we do not report it further here. The third review [52] included the same RCT including people aged up to 22 years in some of its meta-analyses, so we report only results of meta-analyses that do not include that RCT. The first [50] and third reviews [52] identified 5 RCTs in total and three of these were reported in both reviews. Owing to statistical heterogeneity among trials, the most recent systematic review [50] did not perform a meta-analysis, so we report results from individual RCTs here. [54] [55] [56] [57]

Episodes of vomiting

Compared with placebo Ondansetron may be more effective at reducing episodes of vomiting within 24 hours of treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Episodes of vomiting					
[55] RCT	36 children aged 6 months to 8 years who had vomited twice within 1 hour. All children were hospitalised for a minimum of 24 hours. In review [50]	**Mean number of episodes , <24 hours after treatment** 2 with ondansetron 5 with placebo	P = 0.049	○○○	ondansetron
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours. In review [50]	**Mean number of episodes , in the emergency department** 0.18 with ondansetron 0.83 with placebo	P = 0.001	○○○	ondansetron

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Mean number of episodes , <24 hours after treatment** 0.75 with ondansetron 0.96 with placebo	P = 0.96	⟷	Not significant
[56] RCT	215 children aged 6 months to 10 years with non-bloody vomiting within the 4 hours preceding triage, and mild to moderate dehydration In review [50]	**Mean number of episodes , <24 hours after treatment** 0.18 with ondansetron 0.65 with placebo	RR 0.30 95% CI 0.18 to 0.50 P <0.001	●●○	ondansetron
[53] RCT	109 children aged 5 months to 8 years with symptoms of gastroenteritis and who had vomited at least 4 times	**Mean number of episodes of vomiting , 8 hours** 0.36 with ondansetron 1.33 with placebo	P <0.001	○○○	ondansetron
Proportion of children with episodes of vomiting					
[55] RCT	36 children aged 6 months to 8 years who had vomited twice within 1 hour. All children were hospitalised for a minimum of 24 hours In review [50]	**Proportion of children with episodes of vomiting , <24 hours after treatment** 5/12 (42%) with ondansetron 10/12 (83%) with placebo	P = 0.04	○○○	ondansetron
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Proportion of children with episodes of vomiting , in the emergency department** 10/74 (14%) with ondansetron 25/71 (35%) with placebo	P = 0.004	○○○	ondansetron
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Proportion of children with episodes of vomiting , <24 hours after treatment** 27/64 (42%) with ondansetron 26/56 (46%) with placebo	P = 0.8	⟷	Not significant
[56] RCT	215 children aged 6 months to 10 years with non-bloody vomiting within the 4 hours preceding triage, and mild to moderate dehydration In review [50]	**Proportion of children with episodes of vomiting , <24 hours after treatment** 15/107 (14%) with ondansetron 37/107 (35%) with placebo	RR 0.40 95% CI 0.26 to 0.61 P <0.001	●●○	ondansetron
[53] RCT	109 children aged 5 months to 8 years with symptoms of gastroenteritis and who had	**Proportion of children with episodes of vomiting , within 8 hours** 12/55 (22%) with ondansetron	RR 0.33 95% CI 0.19 to 0.56 P <0.001	●●○	ondansetron

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	vomited at least 4 times	36/54 (67%) with placebo			
[52] Systematic review	144 children with vomiting during acute gastroenteritis 2 RCTs in this analysis	**Proportion of children with cessation of vomiting , 24 hours** 44/76 (58%) with ondansetron 32/68 (47%) with placebo	RR 1.22 95% CI 0.89 to 1.67 P = 0.21	⟷	Not significant

No data from the following reference on this outcome. [57]

Admissions to hospital

Compared with placebo Ondansetron may be more effective at reducing admissions to hospital (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Admissions to hospital					
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Admissions to hospital** with ondansetron with placebo Absolute results not reported	P = 0.007	○○○	ondansetron
[56] RCT	215 children aged 6 months to 10 years with non-bloody vomiting within the 4 hours preceding triage, and mild to moderate dehydration In review [50]	**Admissions to hospital** 4/107 (4%) with ondansetron 5/107 (5%) with placebo	RR 0.80 95% CI 0.22 to 2.90 P = 1.00	⟷	Not significant
[57] RCT	106 children aged 1 to 10 years with acute gastritis or acute gastroenteritis who failed oral rehydration treatment In review [50]	**Admissions to hospital** 3/51 (6%) with ondansetron 7/55 (13%) with placebo	Significance not assessed		
[53] RCT	109 children aged 5 months to 8 years with symptoms of gastroenteritis and who had vomited at least 4 times	**Admissions to hospital , within 8 hours** 1/55 (2%) with ondansetron 12/54 (22%) with placebo	RR 0.08 P <0.014	●●●	ondansetron

No data from the following reference on this outcome. [52] [55]

Duration of hospital stay

No data from the following reference on this outcome. [52] [53] [54] [55] [56] [57]

Mortality

No data from the following reference on this outcome. [52] [53] [54] [55] [56] [57]

Adverse effects

Compared with placebo Ondansetron may be associated with an increased risk of episodes of diarrhoea (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Episodes of diarrhoea					
[55] RCT	36 children aged 6 months to 8 years who had vomited twice within 1 hour. All children were hospitalised for a minimum of 24 hours In review [50]	**Episodes of diarrhoea** with ondansetron with placebo Absolute results not reported	P = 0.013	○○○	placebo
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Episodes of diarrhoea , in the emergency department** 0.7 with ondansetron 0.61 with placebo	P = 0.62	⟷	Not significant
[54] RCT	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours In review [50]	**Episodes of diarrhoea , <24 hours after treatment** 4.7 with ondansetron 1.37 with placebo	P = 0.002	○○○	placebo
[56] RCT	215 children aged 6 months to 10 years with non-bloody vomiting within the 4 hours preceding triage, and mild to moderate dehydration In review [50]	**Episodes of diarrhoea** 1.4 with ondansetron 0.5 with placebo	P <0.001	○○○	placebo
[57] RCT	106 children aged 1 to 10 years with acute gastritis or acute gastroenteritis who failed oral rehydration treatment In review [50]	**Median number of episodes of diarrhoea , after discharge** 0 (range 0–20) with ondansetron 0 (range 0–6) with placebo Absolute numbers not reported The return rate for symptom diaries provided for follow-up was low. Telephone follow-up was more successful, but the RCT reported that: "without diaries, it is likely that the estimates for the number of episodes of diarrhoea post-discharge were inaccurate. However, this probably did not favour one group over the other".	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[53] RCT	109 children aged 5 months to 8 years with symptoms of gastroenteritis and who had vomited at least 4 times	**Mean number of episodes of diarrhoea , 24 hours** 5.04 with ondansetron 4.30 with placebo 1 person in the ondansetron group was re-assessed for a distended abdomen and an inability to tolerate oral fluids	P = 0.04	○○○	placebo

No data from the following reference on this outcome. [52]

Further information on studies

[54] The RCT did not recruit the calculated sample size because of the time constraints relating to the gastroenteritis season. Macular rash, without urticaria or respiratory symptoms, was reported in one patient 30 minutes after receiving ondansetron.

[54] The RCT evaluated multiple doses of ondansetron; it found that the first dose was associated with a reduction in the episodes of vomiting, but that no benefit was derived from subsequent doses.

[54] The authors commented that a large proportion of children had spontaneous remission of vomiting, which indicates that the criterion for assessing vomiting severity was too low. The RCT also eliminated children with diarrhoea, which may have resulted in the recruitment of children with gastritis only, rather than gastroenteritis.

[55] Drowsiness occurred in >90% of children in all groups.

[56] No cardiovascular or respiratory events occurred. One child in the placebo group developed urticaria.

[55] [56] The RCTs assessed single doses of ondansetron and found significant reductions in the number of episodes of vomiting.

Comment:

Clinical guide:

Three RCTs found an association between ondansetron and an increased incidence of diarrhoea. [54] [55] [56] However, the reported increase of diarrhoea was between one and two episodes. In developing countries this would be of little clinical significance compared with the reduction in vomiting and the avoidance of the need for intravenous fluids. The results may not be applicable to developing communities where the aetiology of gastroenteritis is different, and where dehydration due to diarrhoea results in higher mortality. The relatively small sample sizes of the RCTs do not allow us to make definite conclusions regarding adverse effects. The systematic reviews did not provide adequate evidence to guide clinicians on the most effective dose or route of administration of ondansetron.

OPTION ZINC New

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Zinc reduces the duration of diarrhoea (but not the total stool volume) compared with placebo in children living mainly in developing countries.
- Most evidence is in children in developing countries. Additional studies are required to assess the benefit in developed countries.
- Zinc may increase vomiting compared with placebo.

Benefits and harms

Zinc versus placebo or no treatment:

We found one systematic review comparing zinc versus placebo or no treatment (search date 2007, 18 RCTs, 11,180 children), [58] and one systematic review comparing zinc versus placebo (search date 2007, 18 RCTs, 6165 children).

[59] The reviews identified 11 RCTs in common. The second review [59] assessed acute and persistent diarrhoea separately; we report results from both reviews below.

Duration of diarrhoea

Compared with placebo Zinc may be more effective at reducing the duration of diarrhoea in children aged up to 5 years mainly in developing countries (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of diarrhoea					
[58] Systematic review	5643 children aged up to 5 years with acute gastroenteritis, mainly in developing countries 13 RCTs in this analysis	**Duration of diarrhoea** with zinc with placebo Absolute numbers not reported See further information on studies regarding heterogeneity between included trials	WMD –0.69 days 95% CI –0.97 days to –0.40 days P <0.0001	○○○	zinc
[59] Systematic review	2741 children aged 1 month to 5 years with acute diarrhoea 9 RCTs in this analysis	**Duration of acute diarrhoea** with zinc with placebo Absolute numbers not reported See further information on studies regarding heterogeneity between included trials	WMD –12.27 hours 95% CI –23.02 hours to –1.52 hours P = 0.025	○○○	zinc

Total stool volume

Compared with placebo Zinc may be no more effective at reducing total stool volume in children aged up to 5 years mainly in developing countries (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total stool volume					
[58] Systematic review	606 children aged up to 5 years with acute gastroenteritis, mainly in developing countries 3 RCTs in this analysis	**Total stool volume** with zinc with placebo Absolute numbers not reported See further information on studies regarding heterogeneity between included trials	SMD –0.38 95% CI –1.04 to +0.27 P value not reported	⟷	Not significant

No data from the following reference on this outcome. [59]

Admissions to hospital

No data from the following reference on this outcome. [58] [59]

Duration of hospital stay

No data from the following reference on this outcome. [58] [59]

Mortality

No data from the following reference on this outcome. [58] [59]

Weight gain

No data from the following reference on this outcome. [58] [59]

Adverse effects

Compared with placebo Zinc may be associated with an increase in vomiting in children aged up to 5 years mainly in developing countries (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Episodes of vomiting					
[58] Systematic review	3156 children aged up to 5 years with acute gastroenteritis, mainly in developing countries 5 RCTs in this analysis	**Proportion of children with episodes of vomiting** with zinc with placebo Absolute numbers not reported See further information on studies regarding heterogeneity between included trials	RR 1.22 95% CI 1.05 to 1.43	●○○	placebo
[59] Systematic review	4727 children aged 1 month to 5 years with acute acute diarrhoea 8 RCTs in this analysis	**Proportion of children with vomiting** 466/2390 (19%) with zinc 275/2337 (12%) with placebo See further information on studies regarding heterogeneity between included trials	RR 1.71 95% CI 1.27 to 2.30 P <0.0004	●○○	placebo

Further information on studies

[58] The review reported significant heterogeneity between included trials reporting the duration of diarrhoea. Possible sources of heterogeneity included nutritional status, causes of diarrhoea, dose of zinc used, and duration of treatment. Three studies were excluded from the meta-analysis as they did not report data as a mean. Methodological quality of trials varied, but most were considered high quality. The review used the Human Development Index to classify country of origin of studies into developed, developing, or under-developed. Most studies were conducted in developing countries with one RCT conducted in a developed country and one RCT conducted in an under-developed country.

[59] The review reported significant heterogeneity among included trials. The review did not report on stool volume, as few trials reported this outcome, and there was heterogeneity between those that did.

Comment: **Clinical guide:**
There is evidence from two systematic reviews that zinc is effective in reducing the duration but not the volume of acute diarrhoea in children in developing communities. Additional studies are needed to determine whether there is benefit in using zinc in children in under-developed and developed communities.

OPTION **PROBIOTICS** New

- For GRADE evaluation of interventions for Gastroenteritis in children, see table, p 62 .
- Probiotics may reduce the duration of diarrhoea in children with gastroenteritis and may reduce hospital stay compared with placebo, with most evidence for *Lactobacillus* species. However, some evidence was of poor quality.

Benefits and harms

Probiotics versus placebo or no treatment:

We found 5 systematic reviews (search dates 2001, [60] 2000, [61] 2007, [62] 2006, [63] and 2003 [64]). The systematic reviews identified 30 RCTs between them. Ten RCTs were reported in more than one review. The other 4 reviews performed different meta-analyses, so we report all below. One review [62] reported on only two RCTs that were also reported in three other reviews, and so we do not report this review further. We also found two subsequent RCTs. [65] [66]

Duration of diarrhoea

Compared with placebo Probiotics may be more effective at reducing the duration of diarrhoea in children with gastroenteritis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of diarrhoea					
[64] Systematic review	231 children with diarrhoea caused by rotavirus 4 RCTs in this analysis Subgroup analysis	**Duration of diarrhoea** with probiotics with placebo or no probiotic Absolute numbers not reported Subgroup analysis of children with diarrhoea caused by rotavirus Probiotics assessed in included RCTs: lactobacilli and *Saccharomyces boulardii*	WMD –38.1 hours 95% CI –68.1 hours to –8.10 hours P = 0.01	○○○	probiotics
[60] Systematic review	679 children aged 1 month to 4 years with acute infectious diarrhoea 7 RCTs in this analysis	**Duration of diarrhoea** with probiotics with placebo Absolute numbers not reported Probiotics assessed in included RCTs: *Lactobacillus GG*, *L reuteri*, *L acidophilus LB*, *Saccharomyces boulardii*, *Streptococcus thermophilus lactis*, *L acidophilus*, and *L bulgaricus*	WMD –20.1 hours 95% CI –26.1 hours to –14.2 hours P value not reported	○○○	probiotics
[60] Systematic review	297 children aged 1 month to 4 years with predominantly rotavirus-confirmed gastroenteritis 4 RCTs in this analysis	**Duration of diarrhoea** with probiotics with placebo Absolute numbers not reported Probiotics assessed in included RCTs: *Lactobacillus GG* and *L reuteri*	WMD –24.8 hours 95% CI –31.8 hours to –17.9 hours P <0.0001	○○○	probiotics
[61] Systematic review	675 children aged <37 months with acute diarrhoea 7 RCTs in this analysis	**Duration of diarrhoea** with probiotics with placebo Absolute numbers not reported Probiotics assessed in included RCTs: *Lactobacillus GG*, killed *L acidophilus*, *L reuteri*, and a mix-	Mean difference 0.7 days 95% CI 0.3 days to 1.2 days P value not reported	○○○	probiotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		ture of *L acidophilus* and *L bulgaricus*			
[63] Systematic review	473 children aged 2 months to 12 years with acute diarrhoea 4 RCTs in this analysis	**Duration of diarrhoea** with *Saccharomyces boulardii* with placebo or no treatment Absolute numbers not reported	WMD –1.1 days 95% CI –1.3 days to –0.83 days P value not reported	○○○	*Saccharomyces boulardii*
[60] Systematic review	731 children aged 1 month to 4 years with acute infectious diarrhoea 8 RCTs in this analysis	**Proportion of children with episodes of diarrhoea , 3 days** 77/381 (20%) with probiotics 167/350 (48%) with placebo Probiotics assessed in included RCTs: *Lactobacillus GG*, *L reuteri*, *L acidophilus LB*, *Saccharomyces boulardii*, *Streptococcus thermophilus lactis*, *L acidophilus*, and *L bulgaricus*	RR 0.43 95% 0.34 to 0.53 P <0.0001	●●○	probiotics
[64] Systematic review	1008 children with diarrhoea 11 RCTs in this analysis	**Proportion of children with episodes of diarrhoea , 3 days** 195/518 (38%) with probiotics 265/490 (54%) with placebo or no probiotic Probiotics assessed in included RCTs: lactobacilli and *Saccharomyces boulardii*	RR 0.68 95% CI 0.54 to 0.85 P <0.0008	●○○	probiotics
[64] Systematic review	895 children with diarrhoea 9 RCTs in this analysis	**Proportion of children with episodes of diarrhoea , 4 days** 79/459 (17%) with probiotics 168/436 (39%) with placebo or no probiotic Probiotics assessed in included RCTs: lactobacilli and *Saccharomyces boulardii*	OR 0.41 95% CI 0.24 to 0.68 P = 0.0006	●●○	probiotics
[63] Systematic review	88 children aged 2 months to 12 years with acute diarrhoea Data from 1 RCT	**Proportion of children with episodes of diarrhoea , 7 days** with *Saccharomyces boulardii* with placebo Absolute numbers not reported	RR 0.25 95% CI 0.08 to 0.83 NNT 5 95% CI 3 to 20 P value not reported	●●○	probiotics
[64] Systematic review	232 children with infectious diarrhoea 4 RCTs in this analysis	**Frequency of stools , day 2** with probiotics with placebo or no probiotic Absolute numbers not reported Probiotics assessed in included RCTs: lactobacilli and *Saccharomyces boulardii*	WMD –1.01 stools 95% CI –1.66 stools to –0.36 stools P <0.003	○○○	probiotics
[64] Systematic review	170 children with infectious diarrhoea 2 RCTs in this analysis	**Frequency of stools , day 3** with probiotics with placebo or no probiotic Absolute numbers not reported Probiotics assessed in included RCTs: lactobacilli and *Saccharomyces boulardii*	WMD –1.12 stools 95% CI –1.79 stools to –0.46 stools P <0.0001	○○○	probiotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[61] Systematic review	122 children aged <37 months with acute diarrhoea 3 RCTs in this analysis	**Frequency of stools , day 2** with probiotics with placebo Absolute numbers not reported Probiotics assessed in included RCTs: *Lactobacillus GG*, killed *L acidophilus*, *L reuteri*, and a mixture of *L acidophilus* and *L bulgaricus*	Mean difference –1.6 stools 95% CI –2.6 stools to –0.7 stools P value not reported	○○○	probiotics
[63] Systematic review	331 children aged 2 months to 12 years with acute diarrhoea 3 RCTs in this analysis	**Number of stools , day 3** with *Saccharomyces boulardii* with placebo or no treatment Absolute numbers not reported	WMD –1.3 stools 95% CI –1.9 stools to –0.63 stools P value not reported	○○○	*Saccharomyces boulardii*
[65] RCT **4-armed trial**	178 children aged 12 to 48 months with acute non-bloody diarrhoea The remaining arms assessed *L acidophilus* capsules and conventional yoghurt Location: Iran	**Number of stools , day 3** 1.3 with yoghurt with *L acidophilus* 2.3 with placebo 80 children in this analysis	P = 0.002	○○○	probiotics
[66] RCT	27 children aged 6 months to 10 years with acute gastroenteritis	**Mean number of stools , day 3** 1.68 with *Saccharomyces boulardii* 3.36 with placebo All children were also given oral rehydration and a lactose-free diet Duration of watery diarrhoea before admission was significantly longer in the active-treatment than in the placebo group (P <0.05)	P <0.05	○○○	probiotics

Duration of hospital stay

Compared with placebo Probiotics may be more effective at shortening hospital stay in children with gastroenteritis (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Duration of hospital stay					
[63] Systematic review	200 children aged 2 months to 12 years with acute diarrhoea Data from 1 RCT	**Duration of hospital stay** with *Saccharomyces boulardii* with placebo or no treatment	WMD –1.0 days 95% CI –1.4 days to –0.62 days P value not reported	○○○	*Saccharomyces boulardii*
[65] RCT **4-armed trial**	178 children aged 12 to 48 months with acute non-bloody diarrhoea The remaining arms assessed yoghurt with *L aci-*	**Duration of hospital stay** 3.4 days with *L acidophilus* capsules 4.0 days with placebo 80 children in this analysis	P = 0.03	○○○	probiotics

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	dophilus and conventional yoghurt Location: Iran				

No data from the following reference on this outcome. [60] [61] [64] [66]

Admissions to hospital

No data from the following reference on this outcome. [60] [61] [63] [64] [65] [66]

Mortality

No data from the following reference on this outcome. [60] [61] [63] [64] [65] [66]

Weight gain

No data from the following reference on this outcome. [60] [61] [63] [64] [65] [66]

Total stool volume

No data from the following reference on this outcome. [60] [61] [63] [64] [65] [66]

Adverse effects

No data from the following reference on this outcome. [60] [61] [67] [63] [64] [65] [66]

Further information on studies

Comment: Owing to significant heterogeneity in many of the outcomes analysed in the systematic reviews, and the poor quality of many RCTs included in the reviews, we recommend that results be interpreted with caution. Three systematic reviews included studies that were not placebo controlled; [67] [63] [64] three systematic reviews reported significant heterogeneity with some outcomes; [60] [67] [64] and two systematic reviews included RCTs of variable quality. [63] [64] One of the subsequent RCTs did not describe adequate allocation concealment. [66] We found one updated meta-analysis (search date 2007) [67] that assessed trials of *Lactobacillus GG* versus placebo, which is awaiting translation and will be included in the next update of this review.

GLOSSARY

Lactose intolerance Malabsorption of lactose can occur for a short period after acute gastroenteritis because of mucosal damage and temporary lactase deficiency.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Zinc New option added, for which we found two systematic reviews. [58] [59] Categorised as Likely to be beneficial.

Probiotics New option added, for which we found 5 systematic reviews [60] [61] [62] [63] [64] and two subsequent RCTs. [65] [66] Categorised as Beneficial.

Ondansetron New evidence added, including one updated Cochrane systematic review. [50] [51] [52] [53] [57] Categorisation unchanged (Likely to be beneficial).

Rotavirus vaccines New evidence added. [18] [21] [22] [23] [24] [25] [26] [27] [28] [37] Categorisation unchanged (Beneficial).

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Competing interests: JRDP and EJE declare that they have no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Gastroenteritis in children.**

Important outcomes	Admissions to hospital, Adverse effects, Adverse events requiring admission to hospital, Duration of diarrhoea, Duration of hospital stay, Episodes of diarrhoea, Episodes of vomiting, Fever, Gastrointestinal adverse effects, Intussusception, Irritability, Life-threatening adverse events, Mortality, Total stool volume, Weight gain								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent acute gastroenteritis in children?									
at least 29 (at least 61,570) [17] [19] [20] [21] [22] [23] [24] [26] [27] [29] [31] [32] [34] [35] [36] [37] [38]	Episodes of diarrhoea	Rotavirus vaccines versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
at least 14 (at least 136,549) [17] [18] [19] [21] [23] [24] [26] [28] [29] [31] [32]	Admissions to hospital	Rotavirus vaccines versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (150,288) [18] [23] [27] [28] [31] [32] [37]	Mortality	Rotavirus vaccines versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no statistical comparison between groups
1 (63,225) [32]	Life-threatening adverse events	Rotavirus vaccines versus placebo	4	–1	0	–1	0	Low	Quality point deducted for use of a composite outcome. Directness point deducted for uncertainty about whether outcomes assessed were disease-related or treatment-related
1 (63,225) [32]	Adverse events requiring admission to hospital	Rotavirus vaccines versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about whether hospital admission was disease-related or treatment-related
2 (131,263) [32] [31] [27]	Intussusception	Rotavirus vaccines versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for small number of events
7 (15,518) [17] [36] [34] [31] [20] [38]	Gastrointestinal adverse effects	Rotavirus vaccines versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for lack of statistical analysis in most RCTs
7 (16,055) [17] [34] [36] [31] [20] [38]	Fever	Rotavirus vaccines versus placebo	4	0	0	0	0	High	
14 (1571) [17] [36] [20]	Irritability	Rotavirus vaccines versus placebo	4	–2	0	0	0	Low	Quality points deducted for weak methods and for no significance assessment in 1 RCT
What are the effects of treatments for acute gastroenteritis in children?									
at least 8 (at least 960) [39] [40]	Duration of diarrhoea	Enteral rehydration versus intravenous rehydration	4	–2	0	–2	0	Very low	Quality points deducted for uncertainties about randomisation and blinding. Directness points deducted for including children of different age ranges, socioeconomic backgrounds, and disease severities, and different modes of oral therapy

Important outcomes	Admissions to hospital, Adverse effects, Adverse events requiring admission to hospital, Duration of diarrhoea, Duration of hospital stay, Episodes of diarrhoea, Episodes of vomiting, Fever, Gastrointestinal adverse effects, Intussusception, Irritability, Life-threatening adverse events, Mortality, Total stool volume, Weight gain								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
9 (687) [39] [40]	Duration of hospital stay	Enteral rehydration versus intravenous rehydration	4	–2	0	–2	0	Very low	Quality points deducted for uncertainties about randomisation and blinding. Directness points deducted for including children of different age ranges, socioeconomic backgrounds, and disease severities, and different modes of oral therapy
11 (645) [39] [40]	Weight gain	Enteral rehydration versus intravenous rehydration	4	–2	0	–2	0	Very low	Quality points deducted for uncertainties about randomisation and blinding. Directness points deducted for including children of different age ranges, socioeconomic backgrounds, and disease severities, and different modes of oral therapy
at least 8 (at least 960) [42] [43] [44] [45] [46] [47]	Duration of diarrhoea	Lactose-free feeds versus feeds containing lactose	4	–1	–1	0	0	Low	Quality point deducted for weak methods. Consistency point deducted as results sensitive to methods of analysis used in meta-analysis
5 (479) [43] [44] [45] [46] [47]	Weight gain	Lactose-free feeds versus feeds containing lactose	4	–1	–1	0	0	Low	Quality point deducted for weak methods. Consistency point deducted for conflicting results between studies
5 (409) [42] [46]	Total stool volume	Lactose-free feeds versus feeds containing lactose	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for heterogeneity between RCTs
6 (976) [49]	Duration of diarrhoea	Loperamide versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting and inclusion of open-label RCTs. Consistency point deducted for conflicting results between studies
4 (505) [55] [54] [56] [53] [52]	Episodes of vomiting	Ondansetron versus placebo	4	0	0	–2	0	Low	Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in 1 RCT
4 (575) [54] [56] [57] [53]	Admissions to hospital	Ondansetron versus placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results among RCTs. Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in 1 RCT
5 (611) [55] [54] [56] [53] [57]	Adverse effects	Ondansetron versus placebo	4	0	0	–2	0	Low	Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in 1 RCT
at least 13 (at least 5643) [58] [59]	Duration of diarrhoea	Zinc versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs. Directness point deducted for restricted population (mainly developing communities)
3 (606) [58]	Total stool volume	Zinc versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs. Directness point deducted for restricted population (mainly developing communities)
at least 8 (at least 4727) [58] [59]	Adverse effects	Zinc versus placebo or no treatment	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs. Directness point deducted for restricted population (mainly developing communities)

Important outcomes	Admissions to hospital, Adverse effects, Adverse events requiring admission to hospital, Duration of diarrhoea, Duration of hospital stay, Episodes of diarrhoea, Episodes of vomiting, Fever, Gastrointestinal adverse effects, Intussusception, Irritability, Life-threatening adverse events, Mortality, Total stool volume, Weight gain								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
at least 13 (at least 1115) [64] [60] [61] [63] [65] [66]	Duration of diarrhoea	Probiotics versus placebo or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for RCTs with weak methods and inclusion of RCTs with no-treatment group in reviews. Directness point deducted for heterogeneity between RCTs
2 (280) [63] [65]	Duration of hospital stay	Probiotics versus placebo or no treatment	4	–2	0	–1	0	Very low	Quality points deducted for RCTs with weak methods and inclusion of RCTs with no-treatment group in reviews. Directness point deducted for heterogeneity between RCTs

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.